Nocturnal Oxyhemoglobin Desaturation and Prognosis in Chronic Obstructive Pulmonary Disease and Late Sequelae of Pulmonary Tuberculosis

Hiroshi Kimura, Akira Suda, Tetsuya Sakuma, Koichiro Tatsumi, Yoshikazu Kawakami, Takayuki Kuriyama and Institutions participating in the Respiratory Failure Research Group in Japan*

We prospectively examined the survival rate of 67 chronic obstructive pulmonary disease (COPD) and 74 late sequelae of pulmonary tuberculosis (TB seq) patients to clarify whether nocturnal oxyhemoglobin desaturation (NOD) could be one of the independent factors determining their mortality. The sleep monitoring of arterial oxygen saturation (SpO2) and pulmonary function tests were assessed in all patients at the time of registration. Forty % of COPD and 24% of TB seq died as the direct result of deterioration of chronic respiratory failure during the 7-year observation period. Cox’s proportional hazards analysis showed that NOD was an independent prognostic factor in both groups, and this was especially prominent when evaluated in terms of sleep lowest SpO2 in COPD and 85% desaturation time in TB seq. No significant prognostic factor was observed among age, vital capacity percent predicted (%VC), forced expiratory volume in one second (FEV1.0 %) and partial pressure of carbon dioxide (PaCO2). We conclude that the degree of NOD can affect mortality in COPD and TB seq.

(Key words: oxygen desaturation, sleep, respiratory failure, mortality)

Introduction

Hypoxemia is a well-recognized poor prognostic factor, and thus is one of the indications for long-term oxygen therapy (LTOT) in respiratory failure (1). The complications of nocturnal oxyhemoglobin desaturation (NOD) as well as pulmonary hypertension and exercise-induced oxyhemoglobin desaturation have also been considered as indicative findings for prescribing LTOT (2–6). However, the clinical interpretation of NOD, i.e., how to use NOD in preparing guidelines for LTOT, has remained incomplete. Furthermore, it has not been determined whether NOD by itself has significant influence on the mortality of patients with chronic obstructive pulmonary disease (COPD) and late sequelae of pulmonary tuberculosis (TB seq). It is conceivable that NOD occurs partly because of the deterioration of underlying pathophysiological conditions which become more manifest during sleep than wakefulness. It is also recognized that the underlying mechanisms responsible for NOD are different between COPD and TB seq; the former may mainly be ascribed to hypoventilation in association with the exacerbated imbalance in ventilation-perfusion ratio (7–8), and the latter may be mostly due to hypoventilation during sleep (6). The purpose of this study was to elucidate whether or not NOD may be an independent prognostic factor in COPD and TB seq.

Methods

Sixty-seven patients with COPD (53 males and 14 females) and 74 with TB seq (49 males and 25 females) were pre...
registered in July 1988, and they were followed up for 7 years in 15 institutions participating in the Respiratory Failure Research Group in Japan. Anthropometric and pulmonary function data at the time of entry are shown in Table 1. The registration form contained the information on age, sex and clinical diagnosis as determined by the attending physicians at each institution. At the start of observation, the following data were provided: the sleep monitoring of arterial oxygen saturation (SpO₂) using pulse oximetry, arterial blood gases while breathing air, vital capacity percent predicted (%VC), FEV₁0% percent predicted (%FEV₁,0) and FEV₁0%/FVC (FEV₁,0%). Patients with sleep apnea syndrome were excluded from this study. Baseline SpO₂ values were obtained in the supine resting position before sleep. The degree of NOD was evaluated in two different ways; the lowest value of SpO₂ observed during sleep, defined as “sleep lowest SpO₂”, and the total time spent with SpO₂ at less than 85%, defined as “85% desaturation time”.

The survival of registered cases, the cause of death if applicable (respiratory failure, cancer, cerebrovascular disease, etc.) and the prescription of LTOT were obtained from each institution every year from 1991 to 1995. Deteriorations of pulmonary function and arterial blood gas levels were different between the COPD and TB seq groups, and the duration of follow-up varied from patient to patient. To normalize these variations as well as to elucidate the intrinsic values of the factors that can influence mortality, Cox’s proportional hazards model was used concerning age, %VC, FEV₁0%, partial pressure of carbon dioxide (PaCO₂), sleep lowest SpO₂ and 85% desaturation time.

**Statistical analysis**

All values were expressed by mean ± SD. Comparison between two groups was performed by the Student’s t-test. Survival rates of both groups for respiratory failure-related death were evaluated using the Kaplan-Meier method, and were compared using the log-rank test. P values <0.05 were considered significant.

**Results**

**Pulmonary function and sleep data**

There was no difference between the two groups in terms of age and partial pressure of oxygen (PaO₂). FEV₁0% was significantly lower in the COPD group, while %VC and %FEV₁,0 was considerably lower in the TB seq group. TB seq patients had higher PaCO₂ values than the COPD patients (Table 1).

**Survival rate**

Among the 67 COPD patients, 37 (55%) died during the observation period, 27 (40%) could be followed up for the duration of the observation period, and 3 (5%) were lost to follow-up. The mean follow-up period was 48.5 ± 24.8 months (5.0–84.0 months). Fifty-one COPD patients (76%) received LTOT during the observation period. The causes of death for the COPD group were exacerbation of respiratory failure and related diseases such as right heart failure, pneumonia and pneumothorax (27 patients; 73% of death cases), cancer (14%), suicide (5%), pneumothorax (3%), cerebral infarction (3%) and acute myocardial infarction (3%).

**Table 1. Anthropometric and Pulmonary Function Data**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Age (yr)</th>
<th>%VC (%)</th>
<th>FEV₁,0% (%)</th>
<th>%FEV₁,0 (%)</th>
<th>PaO₂ (mmHg)</th>
<th>PaCO₂ (mmHg)</th>
<th>PAmean (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>67</td>
<td>63.8 ± 13.5</td>
<td>68.8 ± 21.8</td>
<td>44.9 ± 13.6</td>
<td>41.9 ± 20.1</td>
<td>61.9 ± 10.2</td>
<td>44.9 ± 6.4</td>
<td>22.5 ± 5.9</td>
</tr>
<tr>
<td>TB-seq</td>
<td>74</td>
<td>62.3 ± 6.2</td>
<td>40.3 ± 11.5</td>
<td>70.2 ± 18.8</td>
<td>36.1 ± 10.4</td>
<td>65.4 ± 10.7</td>
<td>50.9 ± 6.7</td>
<td>19.9 ± 4.7</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td>N.S.</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td>N.S.</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

(mean ± SD)

**Table 2. Sleep Data**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Baseline SpO₂ (yr)</th>
<th>Sleep lowest SpO₂ (%)</th>
<th>85% desaturation time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>67</td>
<td>91.8 ± 3.6</td>
<td>78.8 ± 9.0</td>
<td>63.6 ± 119.7</td>
</tr>
<tr>
<td>TB-seq</td>
<td>74</td>
<td>92.2 ± 3.3</td>
<td>72.6 ± 11.7</td>
<td>72.5 ± 115.3</td>
</tr>
<tr>
<td>p value</td>
<td></td>
<td>N.S.</td>
<td>&lt;0.001</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

(mean ± SD)
In the TB seq patients, 23 of 74 (31%) died during the observation period, 44 (59%) were alive, and the outcome was unknown in 7 (9%). The mean follow-up period was 53.9±24.1 months (3.6–84.0 months). Fifty-seven TB seq patients (77%) received LTOT during the observation period. The causes of death for the TB seq group were exacerbation of respiratory failure and related diseases such as right heart failure and pneumonia (18 patients; 78% of death cases), cancer (13%), acute myocardial infarction (4%) and others (4%).

According to the conventional manner of analyzing mortality, patients whose cause of death had no relation with the background diseases were excluded. As a result, 27 COPD patients and 18 TB seq patients were included in the death group, and the other patients were treated as alive or discontinued at the end of the follow-up period.

The cumulative survival rates by Kaplan-Meier method in both groups are shown in Fig. 1. The overall survival rate of the COPD group was significantly lower than that of the TB seq group by the log-rank test (p<0.05).

**Relationship between awake PaO₂ and NOD**

The sleep lowest SpO₂ and the 85% desaturation time plotted against awake PaO₂ in both groups are illustrated in Figs. 2 and 3, respectively. In the TB seq group the regression line between these two variables was located below that of the COPD group. In some of the TB seq patients with awake PaO₂ over 60 mmHg, the sleep lowest SpO₂ values were unexpectedly lower than those expected from the awake PaO₂ in COPD patients. When the variables were analyzed for the whole group including both dead and alive patients, the rates of the TB seq patients whose lowest SpO₂ was 70% or less in the subgroups of 55<PaO₂<60 mmHg and 55<PaO₂<70 mmHg were 46% (6 of 13 cases) and 36% (14 of 39 cases), respectively. Similarly, the rates of the TB seq patients whose 85% desaturation time was greater than 60 minutes in 55<PaO₂<60 mmHg and 55<PaO₂<70 mmHg were 39% (5 of 13 cases) and 33% (13 of 39 cases), respectively.

**Figure 1.** The cumulative survival rates analyzed by the Kaplan-Meier method in COPD and TB seq patients. The overall survival rate of the COPD group was significantly lower than that of the TB seq group by the log-rank test (p<0.05). ---: all TB seq patients, ----: all COPD patients.

**Figure 2.** The sleep lowest SpO₂ plotted against awake PaO₂ in COPD patients (left) and TB seq patients (right). In the TB seq group the regression line between these two variables was located below that in the COPD group. Vertical lines at awake PaO₂ of 55 mmHg and 60 mmHg correspond to the levels of the guidelines for prescribing LTOT in patients with chronic respiratory failure issued by the Japan Society of Chest Diseases, i.e., PaO₂ <55 mmHg in room air at rest, and 55 <PaO₂ <60 mmHg in room air at rest associated with severe hypoxemia during exercise or sleep. Closed circles: death cases; open circles: alive patients and discontinued patients at the end of the follow-up period; arrows: COPD patients with a substantially lower sleep nadir SpO₂ than predicted from the regression line.
Nocturnal Desaturation and Prognosis

**Table 3. Multivariate Analyses of Parameters on Mortality**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group</th>
<th>Beta</th>
<th>SE</th>
<th>χ²</th>
<th>p value</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>COPD</td>
<td>0.012</td>
<td>0.021</td>
<td>0.354</td>
<td>0.552</td>
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<tr>
<td></td>
<td>TB-seq</td>
<td>0.084</td>
<td>0.048</td>
<td>2.993</td>
<td>0.084</td>
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<tr>
<td>%VC</td>
<td>COPD</td>
<td>0.007</td>
<td>0.011</td>
<td>0.369</td>
<td>0.544</td>
</tr>
<tr>
<td></td>
<td>TB-seq</td>
<td>-0.056</td>
<td>0.034</td>
<td>2.74</td>
<td>0.098</td>
</tr>
<tr>
<td>FEV₁₀₅%</td>
<td>COPD</td>
<td>0.005</td>
<td>0.015</td>
<td>0.127</td>
<td>0.722</td>
</tr>
<tr>
<td></td>
<td>TB-seq</td>
<td>0.002</td>
<td>0.016</td>
<td>0.012</td>
<td>0.912</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>COPD</td>
<td>-0.049</td>
<td>0.036</td>
<td>1.855</td>
<td>0.173</td>
</tr>
<tr>
<td></td>
<td>TB-seq</td>
<td>0.064</td>
<td>0.05</td>
<td>1.66</td>
<td>0.198</td>
</tr>
<tr>
<td>Sleep lowest SpO₂</td>
<td>COPD</td>
<td>-0.092</td>
<td>0.032</td>
<td>8.248</td>
<td>0.0041</td>
</tr>
<tr>
<td></td>
<td>TB-seq</td>
<td>0.069</td>
<td>0.03</td>
<td>5.313</td>
<td>0.021</td>
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<tr>
<td>85% desaturation time</td>
<td>COPD</td>
<td>0.001</td>
<td>0.002</td>
<td>0.493</td>
<td>0.482</td>
</tr>
<tr>
<td></td>
<td>TB-seq</td>
<td>0.008</td>
<td>0.003</td>
<td>9.382</td>
<td>0.0022</td>
</tr>
</tbody>
</table>

Cox’s proportional hazards analysis

Cox’s proportional hazards model was used to demonstrate the prognostic factors independent of variables as well as of observation periods (Table 3). The data indicate that the sleep lowest SpO₂ in COPD (p=0.0041) and the 85% desaturation time in TB seq (p=0.0022) were remarkably related to mortality. The sleep lowest SpO₂ was also weakly related to mortality in TB seq (p<0.05). However, no significant prognostic factor was observed in %VC, FEV₁₀₅% and PaCO₂.

Figure 3. The total time spent with SpO₂ of less than 85% (85% desaturation time) plotted against awake PaO₂ in COPD patients (left) and TB seq patients (right). Closed circles: death cases; open circles: alive patients and discontinued patients at the end of follow-up.

39 cases), respectively. On the other hand, the rates of COPD patients whose lowest SpO₂ was 70% or less in the subgroups of 55<PaO₂<60 mmHg and 55<PaO₂<70 mmHg were 25% (3 of 12 cases) and 14% (5 of 37 cases), respectively. Similarly, the rates of COPD patients whose 85% desaturation time was greater than 60 minutes in 55<PaO₂<60 mmHg and 55<PaO₂<70 mmHg were 33% (4 of 12 cases) and 14% (5 of 37 cases), respectively. Moreover, it was observed that the mortality rate among the COPD patients with lower sleep nadir SpO₂ than predicted from the regression line was relatively high (arrows in Fig. 2).
Discussion

In the present study we demonstrated the following points: 1) NOD is one of the independent prognostic factors in both COPD and TB seq patients. 2) Sleep lowest SpO₂ is a general and relevant factor for prognostic indication in both patient groups, and this was especially true in the COPD group. 3) The 85% desaturation time is a reliable prognostic factor in TB seq patients.

In this study, the effect of LTOT on survival rate could not be individually evaluated because almost all institutions started LTOT regardless of the value of daytime PaO₂. As the usefulness of LTOT has already been well established in patients with chronic respiratory failure, it cannot be justified to set up a control group without LTOT. The rates of association of LTOT were very similar in both patient groups: 76% in COPD and 77% in TB seq. To eliminate the influence of with or without LTOT on the present analysis, we applied Cox's proportional hazards model also to the subgroups of patients who received LTOT during their follow-ups. The data demonstrated that the sleep lowest SpO₂ in COPD (p=0.0019) and the 85% desaturation time in TB seq (p=0.0061) were also remarkably related to mortality. From these findings, we assumed that LTOT may essentially not have affected the results of the present analysis of survival rate.

Hypoxemia during sleep may be caused by several physiological as well as pathological changes. It is conceivable that sleep oxyhemoglobin desaturation occurs mainly in association with the deterioration of ventilatory output which may be related to state-specific change, i.e., the differences among wakefulness, non-rapid eye movement (NREM) sleep and REM sleep (9, 10). Induced hypoventilation is known to be most severe during REM sleep, especially at the time of the appearance of bursts of eye movement, as compared with that during NREM sleep in normal subjects (11, 12) as well as in patients with COPD (8, 9, 13). In addition to sleep-related hypoventilation, several additional factors seem to play a role in inducing hypoxemia. It is generally known that, in COPD patients, the dead space is increased even during wakefulness. In such a condition, oxyhemoglobin desaturation would be more clearly elicited in association with the change in breathing pattern such as rapid shallow breathing in REM sleep (9, 14). REM-associated hypopnea also contributes to hypoxemia in such patients. Also, the impairment of ventilation-perfusion mismatching mainly due to the reduction in functional residual capacity possibly contributes to sleep-related hypoxemia in COPD patients (7). Moreover, the loss of intercostal and accessory muscle activity during REM sleep may cause a decrease in lung volume which is likely to be related to airway closure, resulting in the development of units with little ventilation in relation to their perfusion (9). Thus, there is evidence that hypoventilation contributes to sleep hypoxemia in COPD, and this may be accentuated by changes in the distribution of ventilation and perfusion in the lung.

On the other hand, in patients with TB seq, alveolar hypoventilation can easily occur due to other reasons during sleep. Lung compliance decreases because of pleural thickening and postinflammatory pulmonary fibrosis, and also because of the loss of lung volume frequently caused by thoracoplasty in TB seq patients (15, 16). The increase in PaCO₂ has also been reported to contribute to oxyhemoglobin desaturation during sleep through the right-downward shift of the oxyhemoglobin dissociation curve in such patients (6, 17). Their ventilation can be maintained with the recruitment of accessory muscles including the external intercostal muscles so as to avoid the increase in PaCO₂ during wakefulness. Hypoventilation can be easily and predominantly produced during REM sleep in such patients, as the intercostal muscles are selectively suppressed compared with the diaphragm, resulting in severe hypoxemia during sleep. Different contributions by the mechanisms which cause NOD might explain some of the dissimilar relationships between NOD and mortality in the COPD and TB seq patients.

Sakuma et al (6) have reported that the magnitude of NOD was less profound in COPD patients than in TB seq patients even though they had the same levels of awake PaO₂. Nevertheless, the survival rate of COPD patients was significantly lower when the subjects were chosen independently of awake PaO₂ in the present study. At the same time, it was clearly demonstrated that the sleep lowest SpO₂ is an important prognostic factor especially in COPD patients. Our findings suggest that we must pay more attention to the possibility of COPD patients having severe nadir SpO₂ during sleep, and that this might have to be considered an indication for LTOT. As repetitive episodes of transient hypoxemia during sleep are known to cause an increase in pulmonary vascular resistance (3, 18–20), it is likely that the difference in mortality is derived from differences in the level of pulmonary artery pressure and/or pulmonary vascular resistance.

The present study was performed by analyzing factors mainly related to physiological findings including pulmonary functions and diurnal and nocturnal hypoxemia. Due to the limited information from the registration cards, we could not investigate the effects of dyspnea, nutritional status and smoking, which are important known factors affecting survival. The possibility that they also contribute to the prognostic factors in COPD and TB seq patients must be recognized.

In summary, the present study suggests that NOD can be an independent prognostic factor in both COPD and TB seq patients. This was especially the case when evaluated in terms of the sleep lowest SpO₂ in COPD and the 85% desaturation time in TB seq. Observation of sleep oxyhemoglobin desaturation in these patients is clearly important from the viewpoint of long-term outcome.

Acknowledgements: The authors thank Dr. Y. Honda for reading the manuscript. This study was supported in part by a grant from the Research Committee, Intractable Respiratory Failure, the Ministry of Health and Welfare of Japan.

References

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