Predictors for nocturnal hypoxaemia (mean $\text{Sao}_2 < 90\%$) in normoxic and mildly hypoxic patients with COPD

P.J.E. Vos, H.Th.M. Folgering, C.L.A. van Herwaarden

**ABSTRACT:** Detection of nocturnal hypoxaemia, defined as a mean arterial oxygen saturation below 90\%, in normoxic or mildly hypoxic chronic obstructive pulmonary disease (COPD) patients seems clinically relevant, since this feature may precede pulmonary hypertension. Nocturnal studies are expensive and time-consuming procedures. The current study investigates to what extent it is possible to predict nocturnal hypoxaemia from daytime parameters.

Forty-two COPD patients with a daytime arterial oxygen tension ($\text{PaO}_2$) above 8 kPa participated. Nocturnal oxygenation, daytime blood gas values, and ventilatory responses to hypercapnia were measured.

In 10 patients, enough desaturations occurred to qualify as nocturnal hypoxaemia. They had a significantly lower daytime $\text{PaO}_2$ value, and a lower steady-state hypercapnic ventilatory response. They also smoked more often, and complained about daytime sleepiness. Multiple linear regression analysis demonstrated that daytime $\text{PaO}_2$ (32\%) was the best independent predictor. Sleepiness (12\%), and number of cigarettes smoked (5\%) also contributed independently, but in a minor way. Patients with a high daytime $\text{PaO}_2$ (>11 kPa) did not develop nocturnal hypoxaemia.

The hypercapnic ventilatory response was used to distinguish nocturnal hypoxaemia from normoxaemic patients. Only patients with a low response (<3.5 l·min$^{-1}$·kPa$^{-1}$) appeared to run a risk of developing nocturnal hypoxaemia. The sensitivity of this test was 80\%, and the specificity 70\%.

It is concluded that daytime $\text{PaO}_2$, hypercapnic ventilatory response and sleepiness are helpful in predicting nocturnal hypoxaemia.

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Episodes of oxygen desaturation may occur during sleep in patients with chronic obstructive pulmonary disease (COPD) [1-4]. In severe hypoxaemic COPD patients, such episodes are treated adequately when long-term supplemental oxygen is administrated [5-7]. COPD patients with mild daytime hypoxia or normoxia ($\text{PaO}_2 > 8$ kPa) may also have transient oxygen desaturations during sleep, but they may not be apparent to physicians who only evaluate daytime blood gas values [8-10]. Nevertheless, this transient nocturnal hypoxaemia is accompanied by elevated pulmonary artery pressures [1-4, 8, 11-17]. Moreover, it has been suggested that these transient elevations of the pulmonary artery pressure may lead to sustained pulmonary hypertension; and, finally, to the development of right heart failure [8, 12, 14, 17-23].

In practice, it is not feasible to perform expensive nocturnal studies in all COPD patients who are mildly hypoxic or normoxic whilst awake. Therefore, it has been investigated whether daytime characteristics predict oxygenation during sleep in these patients. Levi-Valensii et al. [8] showed a significant relationship between the baseline arterial oxygen saturation ($\text{Sao}_2$) awake and nocturnal $\text{Sao}_2$ in COPD patients with a $\text{PaO}_2$ awake above 8 kPa. Fletcher et al. [10] indicated that the desaturators had lower $\text{PaO}_2$ and higher arterial carbon dioxide tension ($\text{PaCO}_2$) values awake than nondesaturators. Furthermore, Bradley et al. [9] showed that daytime hypercapnia is a risk factor for the development of nocturnal hypoxaemia in COPD patients with mild daytime hypoxaemia. However, all these parameters have appeared to be of little predictive value [8-10].

The purpose of the current study was to evaluate in COPD patients with mild daytime hypoxaemia or normoxia ($\text{PaO}_2 > 8$ kPa), several daytime parameters as possible predictors of nocturnal hypoxaemia. The latter was defined as a mean nocturnal $\text{Sao}_2$ below 90\%.

**Methods**

**Patients**

Forty-two patients with COPD (American Thoracic Society (ATS) criteria [5]) participated in this study. Inclusion criteria were: daytime $\text{PaO}_2$ above 8.0 kPa; and
Table 1. - Characteristics of the COPD patients

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Mean Noct. Sao2 &lt;90%</th>
<th>Mean Noct. Sao2 ≥90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex M/F</td>
<td>39/3</td>
<td>10/0</td>
<td>29/3</td>
</tr>
<tr>
<td>Age yrs</td>
<td>67 (7)</td>
<td>66 (6)</td>
<td>68 (7)</td>
</tr>
<tr>
<td>FEV1 % pred</td>
<td>35 (10)</td>
<td>31 (10)</td>
<td>36 (11)</td>
</tr>
<tr>
<td>TLC % pred</td>
<td>80 (17)</td>
<td>71 (17)</td>
<td>82 (17)</td>
</tr>
<tr>
<td>IVC % pred</td>
<td>100 (22)</td>
<td>98 (32)</td>
<td>100 (18)</td>
</tr>
<tr>
<td>FRC % pred</td>
<td>131 (32)</td>
<td>140 (46)</td>
<td>128 (26)</td>
</tr>
<tr>
<td>RV % pred</td>
<td>146 (43)</td>
<td>163 (65)</td>
<td>141 (33)</td>
</tr>
<tr>
<td>HCVR l-min⁻¹-kPa⁻¹</td>
<td>4.2 (4)</td>
<td>2.1 (2)</td>
<td>4.9 (4.2)*</td>
</tr>
<tr>
<td>Paco2 daytime kPa</td>
<td>9.8 (1.1)</td>
<td>9.1 (0.7)</td>
<td>10.0 (1.1)*</td>
</tr>
<tr>
<td>Paco2 daytime kPa</td>
<td>5.4 (0.7)</td>
<td>5.8 (0.9)</td>
<td>5.3 (0.6)†</td>
</tr>
<tr>
<td>Body mass index</td>
<td>23 (3)</td>
<td>23 (4)</td>
<td>23 (3)</td>
</tr>
<tr>
<td>Smoking %</td>
<td>24%</td>
<td>50%</td>
<td>16%</td>
</tr>
<tr>
<td>Sleepiness %</td>
<td>24%</td>
<td>60%</td>
<td>12%</td>
</tr>
<tr>
<td>Mean noct. Sao2 %</td>
<td>91 (2.3)</td>
<td>88 (1.8)</td>
<td>92 (1.5)*</td>
</tr>
<tr>
<td>Lowest noct. Sao2 %</td>
<td>83 (6.7)</td>
<td>78 (5.7)</td>
<td>85 (5.9)*</td>
</tr>
</tbody>
</table>

Table 2. - Correlations between the mean nocturnal Sao2 and daytime characteristics

<table>
<thead>
<tr>
<th>Sao2 %</th>
<th>PaO2 daytime kPa</th>
<th>HCVR l/min⁻¹-kPa⁻¹</th>
<th>Cigarettes/day</th>
<th>Sleepiness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean nocturnal Sao2</td>
<td>0.56*</td>
<td>0.58*</td>
<td>0.41*</td>
<td>-0.49*</td>
</tr>
</tbody>
</table>

Data are presented as mean (sd). COPD: chronic obstructive pulmonary disease; Noc: nocturnal; M: male; F: female; FEV1: forced expiratory volume in one second; TLC: total lung capacity; IVC: inspiratory vital capacity; FRC: functional residual capacity; RV: residual volume; % pred: percentage of predicted; HCVR: hypercapnic ventilatory response; Paco2: arterial carbon dioxide tension; Sao2: arterial oxygen saturation; Body mass index: body weight (kg)/length² (m). *: p<0.05; †: 0.1 < p < 0.05.

The patients were questioned about the number of cigarettes they smoked daily. Daytime sleepiness was considered to be present when the sleepiness interfered with daily life, or had been noticed by other people.

Night-time. Oxygen saturation (Oxyschuttie, SensorMedics), chest-wall movements (Vitalog), oronasal airflow (thermistors), electromyogram (EMG) of the intercostal muscles, and electro-oculogram (EOG) were recorded from 10 p.m. until 6 a.m. The electromyogram of the 2nd and 3rd parasternal intercostal muscles was recorded with surface electrodes, rectified and integrated. EMG-activity indicated breathing efforts.

The saturation data of the whole night were stored, digitized and analyzed by a computer (Apple IIe) to provide the mean and the lowest saturation of each night. Desaturation was defined as a decrease of more than 4% in oxygen saturation from the asleep baseline Sao2. The asleep baseline Sao2 was defined as the mean saturation 15 min after falling asleep, lying in a horizontal position. Nocturnal hypoxaemia was defined as a mean Sao2 below 90%.

Central apnoea was defined as a cessation of airflow, thoracoabdominal movement, and activity of the intercostal muscles for at least 10 s. Obstructive apnoea was defined as absence of airflow for at least 10 s in the presence of thoracoabdominal movement and intercostal muscle activity.

Indication for rapid eye movement (REM) sleep was shown when regular EOG activity was present.

Statistics

Statistical analyses to compare patient characteristics of the two groups were performed using the Wilcoxon two sample test and the Chi-squared test. Relationships between variables were evaluated with Spearman's rank correlation. Furthermore, partial correlations were determined by multiple linear regression analysis.

Results

In 33 of the 42 patients, one or more nocturnal desaturations occurred. In 10 patients, mean nocturnal oxygen saturation was below 90%. These 10 patients had significantly lower daytime PaO2 values and lower hypercapnic ventilatory responses than the 32 others (table 1). Furthermore, they complained more often about sleepiness. In one patient more than 10 obstructive apneas-h⁻¹ were found.

Table 2. - Correlations between the mean nocturnal Sao2 and daytime characteristics
However, the hypercapnic ventilatory response appeared to be helpful to indicate nocturnal hypoxaemia; and may, therefore, avoid redundant sleep studies. If sleep studies were performed only in those patients with a hypercapnic ventilatory response below 3.5 \textit{l}\textit{m}^{-1}\textit{kPa}^{-1}, two of the nocturnal hypoxaemic patients (20%) would be missed, whereas 8 of the nocturnal normoxic patients (22%) would be measured unnecessarily. One of the two patients with unexpected nocturnal hypoxaemia had an obstructive sleep apnoea/hypopnoea syndrome. The negative predictive value of the test as a screening method in the current study was 91%, which is quite reasonable.

Our results are similar to those demonstrated in hypoxic COPD patients [26, 27]. Patients with higher CO\(_2\) responses were not likely to develop nocturnal hypoxaemia, whereas patients with lower ventilatory responses to CO\(_2\) might or might not have nocturnal hypoxaemia. It suggests that a blunted chemical drive by itself does not necessarily cause the nocturnal hypoxaemia, but allows the hypoxaemia, which is caused by other factors, such as ventilation-perfusion mismatching and changes in functional residual capacity [2], to persist. Other parameters, not measured in this study, but possibly influencing the nocturnal saturation are, for instance, respiratory muscle performance. Not only is the functioning of the central nervous respiratory organization important in this respect, but also the properties of the effector organ; i.e. the respiratory muscles. It was shown by HEYDRA et al. [28] that nocturnal desaturations in COPD patients are also associated with respiratory muscle dysfunction.

The hypercapnic ventilatory response was measured by the steady-state method. In order to restrict the burden on patients due to CO\(_2\)-loading, only two steps of the CO\(_2\)-response curve were measured. A possible drawback of this method may be that it disregards the nonlinearity in the CO\(_2\)-response curve at low Paco\(_2\) levels (dog-leg). However, since most patients were normocapnic or hypercapnic, and since the step in PetCO\(_2\) was rather high, the effect of the slope can only be of minor importance. Furthermore, a nonlinearity of the CO\(_2\) response curve is most prominent in hypoxic conditions. Since our patients were kept normoxic, a nonlinear CO\(_2\) response curve in normoxic and hypercapnic ranges is unlikely.

Only a small number of patients participated in this study, and the cut-off point for the hypercapnic ventilatory response had a low positive predictive value (50%). The validation of the test still has to be established in a prospective study.

The results of this study have some practical implications. Firstly, nocturnal hypoxaemia in patients with a daytime Paco\(_2\) above 11.0 kPa is very unlikely. Secondly, in COPD patients with a daytime Paco\(_2\) below 11.0 kPa and above 8.0 kPa, measurement of the hypercapnic ventilatory response may be helpful as a screening test. Only in patients with responses below 3.5 \textit{l}\textit{m}^{-1}\textit{kPa}^{-1}, are nocturnal studies indicated.

**Discussion**

This study shows that nocturnal hypoxaemia was present in 10 of the 42 patients with normoxia or mild hypoxia. No patient with a Paco\(_2\) above 11.0 kPa developed nocturnal hypoxaemia.

The patients with nocturnal hypoxaemia had a significantly lower Paco\(_2\) value, lower hypercapnic ventilatory response, and more complaints of sleepiness. The large overlap in daytime Paco\(_2\) made it impossible to predict nocturnal hypoxaemia in every individual patient.

**Table 3.** Results of the HCVR as a screening method to distinguish patients with nocturnal hypoxaemia (mean Sao\(_2\) <90%: positive test) and without nocturnal hypoxaemia (mean Sao\(_2\) ≥90%: negative test) (patients with a HCVR below 3.5 \textit{l}\textit{m}^{-1}\textit{kPa}^{-1} were considered prone to nocturnal hypoxaemia)

<table>
<thead>
<tr>
<th>Total</th>
<th>Predicted mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Sao(_2) &lt;90%</td>
</tr>
<tr>
<td>Real</td>
<td>10</td>
</tr>
<tr>
<td>mean Sao(_2) &lt;90%</td>
<td>27</td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
</tr>
</tbody>
</table>

Spearman's rank correlation showed a significant relationship between the mean nocturnal Sao\(_2\) and daytime Sao\(_2\), daytime Pao\(_2\), the hypercapnic ventilatory response, and number of cigarettes smoked daily (table 2). Presence of sleepiness also appeared to be significantly different, indicating that sleepy persons had a lower mean nocturnal desaturation (Chi-squared test, \(p=0.01\)).

The partial correlations to the prediction of the mean nocturnal Sao\(_2\) were determined by multiple linear regression analysis. This showed that daytime Pao\(_2\) (32%), sleepiness (12%), and number of cigarettes smoked (5%), contributed independently to the total variance of 49% of the mean nocturnal Sao\(_2\). The prediction equation was: mean nocturnal Sao\(_2\)=83.3 + 0.89 Pao\(_2\) - 2 sleepiness - 0.24 number of daily cigarettes. \((r = a + bx + cy + dz), in which sleepiness was scored yes=1, or no=0.

No patients with a daytime Pao\(_2\) above 11.0 kPa developed nocturnal hypoxaemia. The large overlap in daytime Pao\(_2\) made it impossible to distinguish between patients with and without nocturnal hypoxaemia.

When the ability of the hypercapnic ventilatory response to separate the nocturnal hypoxaemic and normoxaemic group was examined in the remaining patients with a daytime Pao\(_2\) below 11.0 kPa, a cut-off point for the hypercapnic ventilatory response below 3.5 \textit{l}\textit{min}^{-1}\textit{kPa}^{-1}, two of the nocturnal hypoxaemic patients (20%) would be missed, whereas 8 of the nocturnal normoxic patients (22%) would be measured unnecessarily. One of the two patients with unexpected nocturnal hypoxaemia had an obstructive sleep apnoea/hypopnoea syndrome. The negative predictive value of the test as a screening method in the current study was 91%, which is quite reasonable.

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References