Predictors for nocturnal hypoxaemia (mean SaO₂ <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 (PaO₂) 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 PaO₂ 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 PaO₂ (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 PaO₂ (>11 kPa) did not develop nocturnal hypoxaemia.

The hypercapnic ventilatory response was used to distinguish nocturnal hypoxaemic 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 PaO₂, hypercapnic ventilatory response and sleepiness are helpful in predicting nocturnal hypoxaemia.

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 (Oxyshuttle, 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 analysed 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 apnoeas-h⁻¹ were found.
Table 3. – Results of the HCVR as a screening method to distinguish patients with nocturnal hypoxaemia (mean SaO2 <90%; positive test) and without nocturnal hypoxaemia (mean SaO2 ≥90%; negative test) (patients with a HCVR below 3.5 l·min⁻¹·kPa⁻¹ were considered prone to nocturnal hypoxaemia)

<table>
<thead>
<tr>
<th>Total Predicted mean SaO2 &lt;90%</th>
<th>SaO2 ≥90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
</tr>
<tr>
<td>Real</td>
<td></td>
</tr>
<tr>
<td>mean SaO2 &lt;90%</td>
<td>10</td>
</tr>
<tr>
<td>mean SaO2 ≥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 SaO2 and daytime SaO2, daytime PaO2, 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 SaO2 were determined by multiple linear regression analysis. This showed that daytime PaO2 (32%), sleepiness (12%), and number of cigarettes smoked (5%), contributed independently to the total variance of 49% of the mean nocturnal SaO2. The prediction equation was: mean nocturnal SaO2 = 83.3 + 0.89 PaO2 - 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 PaO2 above 11.0 kPa developed nocturnal hypoxaemia. The large overlap in daytime PaO2 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 PaO2 below 11.0 kPa, a cut-off point for the response of 3.5 l·min⁻¹·kPa⁻¹ was calculated to yield the highest sensitivity in the prediction of nocturnal hypoxaemia. The results of the hypercapnic ventilatory response as a screening test are shown in table 3. Two patients were falsely classified as not having nocturnal hypoxaemia. Eight patients were falsely classified as having nocturnal hypoxaemia. The sensitivity of this test was 80%, and the specificity 70%. The negative predictive value was 91%, and the positive predictive value 50%.

**Discussion**

This study shows that nocturnal hypoxaemia was present in 10 of the 42 patients with normoxia or mild hypoxia. No patient with a PaO2 above 11.0 kPa developed nocturnal hypoxaemia.

The patients with nocturnal hypoxaemia had a significantly lower PaO2 value, lower hypercapnic ventilatory response, and more complaints of sleepiness. The large overlap in daytime PaO2 made it impossible to predict nocturnal hypoxaemia in every individual patient. 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 l·min⁻¹·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 CO2 responses were not likely to develop nocturnal hypoxaemia, whereas patients with lower ventilatory responses to CO2, 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 of patients due to CO2-loading, only two steps of the CO2-response curve were measured. A possible drawback of this method may be that it disregards the nonlinearity in the CO2-response curve at low PacO2 levels (dog-leg). However, since most patients were normocapnic or hypercapnic, and since the step in PETCO2 was rather high, the effect of the slope can only be of minor importance. Furthermore, a nonlinearity of the CO2 response curve is most prominent in hypoxic conditions. Since our patients were kept normoxic, a nonlinear CO2 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 PaO2 above 11.0 kPa is very unlikely. Secondly, in COPD patients with a daytime PaO2 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 l·min⁻¹·kPa⁻¹, are nocturnal studies indicated.

**Acknowledgement:** The authors would like to express their gratitude to Th.M. de Boo and W.A.J.G. Lemmens for statistical assistance.
References


