Prediction of oxygenation during sleep in patients with chronic obstructive lung disease

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ABSTRACT The accuracy of a prediction equation for assessing the lowest arterial oxygen saturation (Sao₂) during sleep was determined in 24 consecutive patients with chronic obstructive lung disease referred for assessment for home oxygen therapy. Subjects had a mean (SD) FEV₁ of 0·81 (0·31) litre and an FEV₁/FVC of 37% (12%). There was reasonable agreement between predicted and measured values (mean difference [predicted–measured] = -2·5%) but the prediction was not precise as the 95% confidence interval for the difference was +8% to -13%. The duration of arterial oxygen desaturation, defined as the percentage of total sleep time spent below a given Sao₂, was not predicted accurately. It is concluded that nocturnal arterial oxygen desaturation in individual patients with chronic obstructive lung disease cannot be predicted from “awake” measurements with sufficient accuracy to be clinically useful.

Hypoxaemic patients with chronic obstructive lung disease are often prescribed continuous home oxygen on the basis of daytime measurements made with the subject awake. Indications include significant, persistent hypoxaemia (arterial oxygen tension (Pao₂) < 56 mm Hg (7·5 kPa) on two occasions at least three weeks apart), or hypoxaemia (Pao₂ 56–59 mm Hg (7·5–7·9 kPa) accompanied by polycythaemia or right heart failure.1-3 It has been postulated that patients without appreciable daytime hypoxaemia may have nocturnal desaturation severe enough to lead eventually to polycythaemia and cor pulmonale.4-6 If such patients are to be prescribed oxygen, sleep studies would be required unless oxygenation during sleep could be predicted accurately.7 “Awake” oxygen saturation (Sao₂) and lowest Sao₂ recorded during sleep are correlated in patients with chronic obstructive lung disease,8-11 and Connaughton and associates12 recently described an equation that predicted the lowest oxygen saturation during sleep (lowest Sao₂ asleep (%) = 1·98 Sao₂ awake – 103, r = 0·82). The present study was designed to examine whether by using this equation arterial desaturation during sleep could be accurately predicted from measurements made when the subject was awake.

Methods

Twenty four consecutive patients with chronic obstructive lung disease who were referred for assessment of their suitability for home oxygen therapy were studied during sleep. Patients had chronic airflow obstruction (FEV₁ <70% predicted; FEV₁/FVC <60%) with no appreciable improvement after nebulised bronchodilator. No patient had asthma, left ventricular failure, or symptoms suggestive of obstructive sleep apnoea. All patients gave informed consent for the study.

CLINIC VISIT

After a history had been obtained and physical examination performed all patients underwent routine pulmonary function testing, including measurements of lung volumes by body plethysmography and carbon monoxide gas transfer by a single breath method. Spirometry was performed before and 15 minutes after inhalation of 5 mg of nebulised salbutamol. Arterial blood was drawn from the radial artery while the patient was seated after resting for 15 minutes and analysed for pH, oxygen tension (P O₂), and carbon dioxide tension (P CO₂), standard electrodes being used (Radiometer ABL-2). In addition, arterial oxygen saturation was measured with an ear oximeter (Biox IIA, Ohmeda, Colorado). If resting Sao₂ was less than 90%, the oxygen flow rate required to achieve an Sao₂
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of at least 90% was recorded. Haemoglobin concentration was measured from a venous blood sample.

SLEEP STUDIES

Sleep studies were performed one to three weeks after the clinic visit, on two consecutive nights in the sleep laboratory. Patients were randomly allocated to receive either compressed air or supplemental oxygen by nasal prongs on the first night and the other gas mixture on the second night. The patient did not know the order in which the gas mixtures were inhaled. On the air night the flow rate was maintained at 1 litre/minute. On the oxygen night the initial flow rate with the patient lying awake was 0.5 l/min. Flow was increased by 0.5 l/min every 10 minutes until Sao2 was at least 90%, and it was further increased in 0.5 l/min steps during sleep if Sao2 fell below 90% for 10 minutes or more, the aim being to keep this above 90% throughout the night.

The sleep stage was monitored with cup electrodes in standard positions for electroencephalography, chin electromyography, and electro-oculography. Arterial oxygen saturation was continuously monitored by an ear oximeter (Biox II A). Respiratory movements of chest and abdomen were measured by an inductance plethysmograph (Respiritac Corporation, Ardsley, New York). Airflow at the nose and mouth was measured by thermocouples taped to the face. Electrocardiographic monitoring was carried out continuously. All signals were recorded on a 12 channel ink pen recorder (Model 78, Grass Instruments, Quincy, Massachusetts). The oximeter signal was also processed and stored by a desk top computer (Hewlett Packard 47804A, Waltham, Massachusetts) for later construction of frequency distributions of Sao2 during sleep.

Sleep was staged by the method of Rechtschaffen and Kales. Oxygenation was assessed by analysing cumulative time — Sao2 plots to determine percentage of total sleep time spent at or below defined levels of arterial saturation (for example, the percentage of total sleep time spent at or below an Sao2 of 85% is referred to as TST<85>. Lowest arterial saturation during sleep was determined directly from the record. Apnoeic events were categorised as obstructive, central, or mixed according to standard criteria.

ANALYSIS OF RESULTS

Correlations between awake and asleep measurements were assessed by linear (Pearson) correlation or by Spearman rank correlation as appropriate. Computations were carried out with a Microstat program (4-1, Ecosoft, Inc, Indianapolis). Comparisons were made with a Microstat program (4-1, Ecosoft, Inc, Indianapolis). Comparisons were made with a Microstat program (4-1, Ecosoft, Inc, Indianapolis). Comparisons were made with a Microstat program (4-1, Ecosoft, Inc, Indianapolis). Comparisons were made with a Microstat program (4-1, Ecosoft, Inc, Indianapolis). Comparisons were made with a Microstat program (4-1, Ecosoft, Inc, Indianapolis). Comparisons were made with a Microstat program (4-1, Ecosoft, Inc, Indianapolis). Comparisons were made with a Microstat program (4-1, Ecosoft, Inc, Indianapolis). Comparisons were made with a Microstat program (4-1, Ecosoft, Inc, Indianapolis). Comparisons were made with a Microstat program (4-1, Ecosoft, Inc, Indianapolis). Comparisons were made with a Microstat program (4-1, Ecosoft, Inc, Indianapolis). Comparisons were made with a Microstat program (4-1, Ecosoft, Inc, Indianapolis). Comparisons were made with a Microstat program (4-1, Ecosoft, Inc, Indianapolis).

Table 1 Anthropometric and physiological characteristics of the 24 patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
<th>Range</th>
</tr>
</thead>
</table>
| Age (y)                   | 63    | 9.6  | 42 - 74
| Body mass index (kg/m²)   | 23.0  | 3.9  | 17 - 29
| Haemoglobin (g/dl)        | 15.6  | 2.1  | 11.4 - 14.4
| Packed cell volume         | 0.47  | 0.07 | 0.35 - 0.61
| pH                        | 7.43  | 0.04 | 7.35 - 7.56
| PO2 (mm Hg)               | 57    | 9.0  | 41 - 82
| PCO2 (mm Hg)              | 44    | 8.9  | 31 - 62
| Plasma bicarbonate (mmol/l)| 29.1  | 5.6  | 22 - 39.6
| Sao2 (%)                  | 89    | 4    | 80 - 96
| FEV₁ (l)                  | 0.81  | 0.31 | 0.45 - 1.50
| FEV₁ (% pred)             | 32    | 12   | 17 - 62
| FVC (%)                   | 2.27  | 0.67 | 1.0 - 3.85
| FVC (% pred)              | 67    | 16   | 35 - 121
| RV (% pred)               | 204   | 61   | 100 - 334
| TLC (% pred)              | 120   | 24   | 80 - 183
| TLC (%)                   | 57    | 34   | 6 - 120

*Body mass index = weight (kg)/height (m)² (> 30 = obese).
Conversion: traditional to SI units—Blood gas tensions: 1 mm Hg ≈ 0.133 kPa.
PO2, PCO2—arterial oxygen and carbon dioxide tensions; Sao2—arterial oxygen saturation; FVC—forced vital capacity; RV—residual volume; TLC—total lung capacity; TLco—carbon monoxide transfer factor.

Connaughton et al. Accuracy of the prediction was considered in terms of bias and precision, bias being defined as the mean difference between predicted and measured values and precision as the 95% confidence interval for the difference. The agreement between predicted and measured values was assessed by the method described by Bland and Altman.

Results

We studied 24 patients (15 of them men; age range 42–74 years), all of whom had airways obstruction. Three patients had clinical and radiographic evidence of bronchiectasis; of the remaining 21 patients, five had normal values for carbon monoxide transfer factor and 16 had reduced values. Table 1 shows the mean anthropometric data, haemoglobin concentration, arterial blood gas tensions, and pulmonary function.

Table 2 Sleep architecture on the compressed air night in the 24 patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep latency (min)</td>
<td>40</td>
<td>26</td>
</tr>
<tr>
<td>Total sleep period (TSP)* (min)</td>
<td>327</td>
<td>55</td>
</tr>
<tr>
<td>Total sleep time (TST)* (min)</td>
<td>213</td>
<td>82</td>
</tr>
<tr>
<td>Time awake (% TSP)</td>
<td>36</td>
<td>19</td>
</tr>
<tr>
<td>Sleep stage:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 (% TSP)</td>
<td>15</td>
<td>7</td>
</tr>
<tr>
<td>II (% TSP)</td>
<td>28</td>
<td>14</td>
</tr>
<tr>
<td>3 and 4 (% TSP)</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>REM (% TSP)</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Brief arousals/hour TST</td>
<td>5.4</td>
<td>4.6</td>
</tr>
<tr>
<td>Arousals to wakefulness/hour TSP</td>
<td>1.7</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*Time from sleep onset to final awakening.
†TSP minus time of intervening wakefulness.
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for the group. Four patients were current cigarette smokers, 19 were ex-smokers, and one had never smoked. Nine patients had a PaO2 less than 56 mm Hg (7.5 kPa) while awake; of these, seven had a history of right heart failure. Five patients had a PaO2 in the range 56–60 mm Hg (7.5–8.0 kPa), of whom two had had right heart failure. Eleven patients had hypercapnia (PaCO2 > 43 mm Hg (5.7 kPa)). Seven of the nine patients with a history of right heart failure had electrocardiographic evidence of right ventricular hypertrophy or dilated right ventricle from echocardiography. Six patients had secondary polycythaemia and one patient had relative polycythaemia with a reduced plasma volume.

Sleep quality on the compressed air night is shown in table 2. All but one patient had REM sleep. No patient had more than five episodes of obstructive apnoea per hour of sleep. The mean (SD) lowest SaO2 in non-REM sleep was 83.3% (7.0%) and mean (SD) lowest SaO2 in REM sleep was 77.0 (10.0%).

Figure 1 shows the relationship between the lowest SaO2 measured during sleep and the predicted lowest SaO2 during sleep, on the basis of the equation of Connaughton et al.12 In most patients the lowest SaO2 measured during sleep was higher than the predicted value. In figure 2 the difference between predicted and measured lowest SaO2 during sleep is compared with the average lowest SaO2 during sleep. This illustrates the degree of disagreement between measured and

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**Fig 1** Lowest arterial oxygen saturation (SaO2) measured during sleep plotted against lowest SaO2 predicted from the equation of Connaughton et al.12 The line of identity is shown on the figure.

**Fig 2** Difference between the predicted and the measured lowest arterial oxygen saturation (SaO2) during sleep versus the average lowest SaO2 during sleep. Dashed lines represent the mean difference (mean + 2 SD and mean - 2 SD).
Predicted values. The mean difference (predicted—
measured) was −2.5% (95% confidence limits −0.4% to −4.7%). The standard deviation of the
difference was 5.1%. The upper limit of agreement
(mean difference +2 SD) was +8% (95% confidence
limits +4% to +12%) and the lower limit of agreement
(mean difference −2 SD) was −13% (95% confidence
limits −9% to −17%).

The mean (SEM) % TST spent below 85% Sao2
(TST <85%) and 75% Sao2 was 38(9)% and 6(3)%
respectively. The duration of desaturation (TST<85)
was related to awake Sao2 (Spearman rank correlation
(rs) = −0.82), but the prediction equation obtained
by linear regression was not useful (r2 = 0.53). The
patient’s packed cell volume was related to the lowest
Sao2 during sleep (rs = −0.46, p < 0.05) and to the
duration of nocturnal desaturation (rs = 0.50, p <
0.02), but not to awake Sao2 or PaO2.

Multiple stepwise regression analysis using awake
Sao2, PaO2, PaCO2, packed cell volume and lowest Sao2
during sleep showed that only awake Sao2 and packed

cell volume were independent predictors of lowest
Sao2 during sleep (multiple R = 0.90). Figure 3 shows
the relation between the lowest Sao2 during sleep and
Sao2 measured by ear oximetry with the subject sitting,
awake, on the night of the study. The regression
equation and 95% confidence limits for the predicted
lowest Sao2 asleep are shown in the figure. A similar
relation was found between awake Sao2 measured in
the clinic three weeks before the study and the lowest
Sao2 during sleep (lowest Sao2 during sleep = 2.4 ×
awake Sao2 −137; r2 = 0.76).

In five patients the oxygen flow rate required to
maintain Sao2 above 90% during sleep was at least 1.0
l/min more than that required to maintain Sao2 above
90% while subjects were awake. Only one patient,
however, required an addition of more than 1.5 l/min.
Thus an empirically determined addition of 1.5 l/min
to the “awake” oxygen flow rate would have main-
tained Sao2 above 90% during sleep in 23 out of 24
patients.

Discussion

In 24 consecutive patients with chronic obstructive
lung disease referred for home oxygen therapy we
found wide confidence limits for the difference
between Sao2 measured during sleep and values
obtained from a prediction equation based on Sao2
measured with the subject awake. When applied to
large numbers of patients with chronic obstructive
lung disease therefore the equation is not likely to
identify those who have arterial oxygen desaturation
during sleep with sufficient accuracy to be clinically
useful.

The patients in the present study did not sleep as
well as patients with chronic obstructive lung disease
studied by others. All but one patient in the
present study, however, had REM sleep and the depth
and duration of nocturnal arterial oxygen desatura-
tion were similar to those reported previously. We
are unlikely to have underestimated the severity of
nocturnal oxygen desaturation in our patients.

In the study of Connaughton and associates2 Sao2
was measured with a Hewlett Packard 47201A ear
oximeter, whereas we used a Biox IIA oximeter.
Recently, West and associates9 compared the Hewlett
Packard 47201A ear oximeter with the Biox III ear
oximeter during rapid oscillations in Sao2 in patients
with obstructive sleep apnoea. They found that the
Biox pulse oximeter measurements were generally
higher than those simultaneously recorded by the
Hewlett Packard transmittance oximeter. The
difference between the mean lowest Sao2 values re-
corded by the two oximeters was 3%. Although rapid
changes in Sao2 during sleep did not occur frequently
in the patients we studied, the use of a Biox IIA rather
than a Hewlett Packard 47201A oximeter may explain
part of the bias between measured and predicted
values in our study. It is, however, unlikely to explain
the lack of precision that we observed.

We confirmed the close relationship between lowest
Sao2 during sleep and “awake” Sao24–14 and found
prediction equations similar to that of Connaughton
and associates12. The oximeter Sao2 measured in
the clinic one to three weeks before the sleep study was
similar in predictive accuracy to the Sao2 measured by
the oximeter with subjects sitting and awake on the
night of the study (r2 = 0.76 and 0.64 respectively). We
also confirmed the relation between duration of
desaturation during sleep (TST<85) and awake Sao2,
but we found that the awake Sao$_2$ was a poor predictor of TST$_{<85}$ ($r^2 = 0.53$). The oxygen flow rate required to maintain Sao$_2$ at over 90% during sleep could not be predicted accurately; but the addition of 1·5 l/min (an amount decided empirically) to the oxygen flow rate required to achieve an arterial oxygen Sao$_2$ of 90% while the patient was awake would have been adequate during sleep in most cases.

Several issues relating to the clinical utility of a prediction equation for prescribing home oxygen have to be considered. Firstly, in the absence of daytime hypoxaemia, are episodes of nocturnal hypoxaemia harmful? The opinion of the American Thoracic Society is as follows: "Though it is not established that such episodes are harmful, it is probably unwise to assume that they are harmless, and we believe nocturnal oxygen therapy can be justified in such episodes." On the other hand, there is evidence that the extent of nocturnal hypoxaemia is not clinically important. At the present, therefore, the clinical importance of "isolated" nocturnal hypoxaemia is controversial and largely unknown.

The second issue is the precision of the prediction equation for lowest Sao$_2$ during sleep. Let us assume for a moment that "significant" nocturnal hypoxaemia (Sao$_2$ below, say, 75%) should be treated with supplemental oxygen, as has been proposed by Anthonisen. According to the prediction equation, a patient whose Sao$_2$ is 94% while he is awake has a predicted lowest Sao$_2$ during sleep of 83%, with a 95% confidence interval of 75–96%. Similarly, a patient whose Sao$_2$ is 83% while he is awake has a predicted lowest Sao$_2$ during sleep of 61%, with a 95% confidence interval of 53–74% Sao$_2$. A patient whose Sao$_2$ is over 93% while he is awake is therefore most unlikely to have nocturnal arterial oxygen saturation below 75%, whereas if it is below 84% he is almost certain to do so. With an awake Sao$_2$ of 84–93%, however, nocturnal oxygen saturation may drop to 75%, but this cannot be predicted with sufficient precision to be useful in clinical decision making. In the present study seven of the 15 patients with an Sao$_2$ of 84–93% while awake had a lowest Sao$_2$ of less than 75% during sleep. Since this range of arterial oxygen saturation is very common in patients presenting for consideration for home oxygen therapy, the prediction equation is not likely to be helpful in the very population that might benefit from screening before further detailed investigation during sleep is undertaken.

Which patients with chronic obstructive lung disease should have a sleep study? Those with obesity, snoring, morning headaches, and daytime somnolence who are suspected of having the obstructive sleep apnoea syndrome should be studied during sleep. Patients who qualify for continuous home oxygen therapy on the basis of measurements made while they are awake do not require a sleep study since nocturnal oxygen flow rates can be effectively prescribed in an empirical fashion in most cases. If home oxygen therapy is to be prescribed to patients who do not qualify for oxygen therapy on the basis of awake measurements, but who are suspected of having nocturnal hypoxaemia because of polycythaemia, right heart failure, or hypercapnia, a formal sleep study to document the extent of arterial oxygen desaturation during sleep may be required. The efficacy of home oxygen therapy in this group of patients has not, however, been established in a long term, randomised clinical trial.

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