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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 (Sao_2) 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) FEV_1 of 0·81 (0·31) litre and an FEV_1/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 Sao_2, 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 (Pao_2) < 56 mm Hg (7·5 kPa) on two occasions at least three weeks apart), or hypoxaemia (Pao_2 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 (Sao_2) and lowest Sao_2 recorded during sleep are correlated in patients with chronic obstructive lung disease,[8–11] and Connaughton and associates[12] recently described an equation that predicted the lowest oxygen saturation during sleep (lowest Sao_2 asleep (%) = 1·98 Sao_2 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.

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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 (FEV_1 < 70% predicted; FEV_1/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 (Po_2), and carbon dioxide tension (Pco_2), standard electrodes being used (Radiometer ABL-2). In addition, arterial oxygen saturation was measured with an ear oximeter (Biox IIA, Ohmeda, Colorado). If resting Sao_2 was less than 90%, the oxygen flow rate required to achieve an Sao_2

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 Sao_2 was at least 90%, and it was further increased in 0·5 l/min steps during sleep if Sao_2 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.[13] Arterial oxygen saturation was continuously monitored by an ear oximeter (Biox IIA). Respiratory movements of chest and abdomen were measured by an inductance plethysmograph (Respitrace 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 Sao_2 during sleep.

Sleep was staged by the method of Rechtschaffen and Kales.[13] Oxygenation was assessed by analysing cumulative time – Sao_2 plots[14] 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 Sao_2 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.[15]

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 between the lowest recorded Sao_2 during sleep and that predicted from measurement of Sao_2 in the awake subjects were made on the basis of the prediction equation of Connaughton *et al.*[12] 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.[16] The agreement between predicted and measured values was assessed by the method described by Bland and Altman.[17]

Table 1 *Anthropometric and physiological characteristics of the 24 patients*

	Mean	SD	Range
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 – 19·4
Packed cell volume	0·47	0·07	0·35– 0·61
pH	7·43	0·04	7·35– 7·56
Pao_2 (mm Hg)	57	9·0	41 – 82
$Paco_2$ (mm Hg)	44	8·9	31 – 62
Plasma bicarbonate (mmol/l)	29·1	5·6	22 – 39·6
Sao_2 (%)	89	4	80 – 96
FEV_1 (l)	0·81	0·31	0·45– 1·50
FEV_1 (% pred)	32	12	17 – 62
FVC (l)	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
TLCO (% pred)	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.
Pao_2, $Paco_2$—arterial oxygen and carbon dioxide tensions; Sao_2—arterial oxygen saturation; FVC—forced vital capacity; RV—residual volume; TLC—total lung capacity; TLCO—carbon monoxide transfer factor.

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*

	Mean	SD
Sleep latency (min)	40	26
Total sleep period (TSP)* (min)	327	55
Total sleep time (TST)† (min)	213	82
Time awake (% TSP)	36	19
Sleep stage:		
I (% TSP)	15	7
II (% TSP)	28	14
3 and 4 (% TSP)	7	6
REM (% TSP)	14	9
Brief arousals/hour TST	5·4	4·6
Arousals to wakefulness/hour TSP	1·7	0·7

*Time from sleep onset to final awakening.
†TSP minus time of intervening wakefulness.

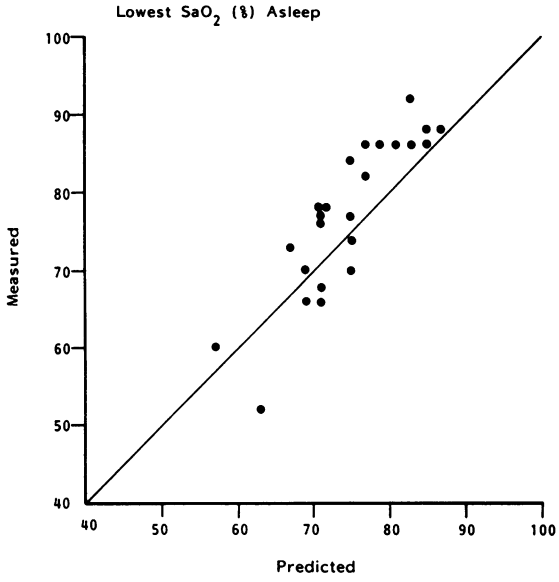

Fig 1 *Lowest arterial oxygen saturation (Sao_2) measured during sleep plotted against lowest Sao_2 predicted from the equation of Connaughton et al.[12] The line of identity is shown on the figure.*

for the group. Four patients were current cigarette smokers, 19 were ex-smokers, and one had never smoked. Nine patients had a Pao_2 less than 56 mm Hg (7·5 kPa) while awake; of these, seven had a history of right heart failure. Five patients had a Pao_2 in the range 56–60 mm Hg (7·5–8·0 kPa), of whom two had had right heart failure. Eleven patients had hypercapnia ($Paco_2$ >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 Sao_2 in non-REM sleep was 83·3% (7·0%) and mean (SD) lowest Sao_2 in REM sleep was 77·0 (10·0)%.

Figure 1 shows the relationship between the lowest Sao_2 measured during sleep and the predicted lowest Sao_2 during sleep, on the basis of the equation of Connaughton *et al.*[12] In most patients the lowest Sao_2 measured during sleep was higher than the predicted value. In figure 2 the difference between predicted and measured lowest Sao_2 during sleep is compared with the average lowest Sao_2 during sleep.[17] This illustrates the degree of disagreement between measured and

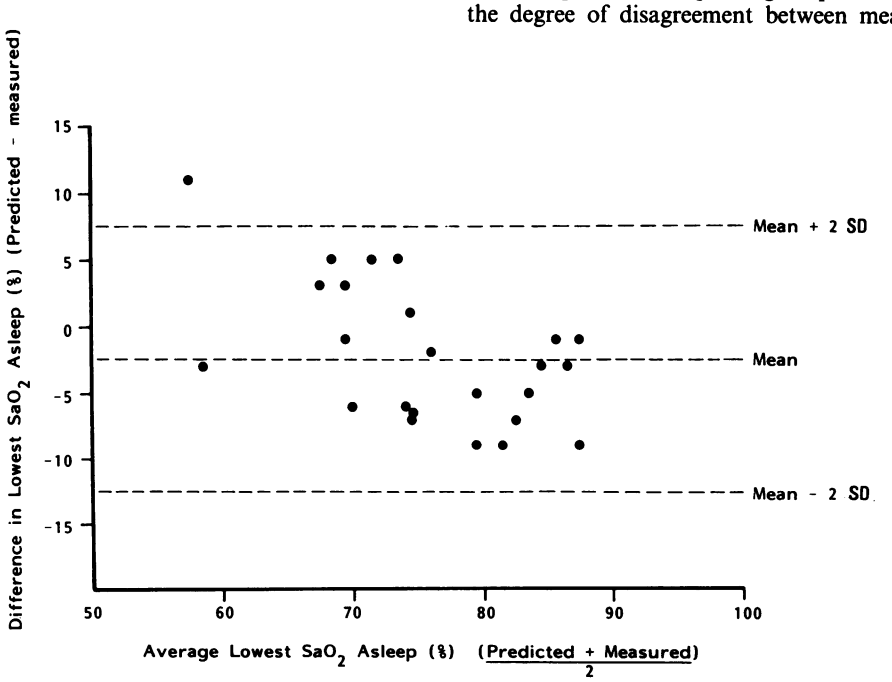

Fig 2 *Difference between the predicted and the measured lowest arterial oxygen saturation (Sao_2) during sleep versus the average lowest Sao_2 during sleep. Dashed lines represent the mean difference (mean + 2 SD and mean −2 SD).*

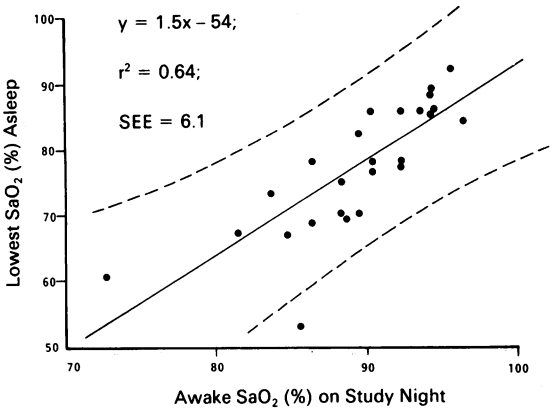

Fig 3 *Lowest arterial oxygen saturation (Sa_{O_2}) during sleep plotted against Sa_{O_2} measured sitting, with the patients awake, on the night of the study with 95% confidence intervals for the predicted lowest Sa_{O_2}.*

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% Sa_{O_2} (TST <85%) and 75% Sa_{O_2} was 38(9)% and 6% (3)% respectively. The duration of desaturation ($TST_{<85}$) was related to awake Sa_{O_2} (Spearman rank correlation (rs) = −0·82), but the prediction equation obtained by linear regression was not useful (r^2 = 0·53). The patient's packed cell volume was related to the lowest Sa_{O_2} during sleep (r_s = −0·46, $p < 0·05$) and to the duration of nocturnal desaturation (r_s = 0·50, $p < 0·02$), but not to awake Sa_{O_2} or Pa_{O_2}.

Multiple stepwise regression analysis using awake Sa_{O_2}, Pa_{O_2}, Pa_{CO_2}, packed cell volume and lowest Sa_{O_2} during sleep showed that only awake Sa_{O_2} and packed cell volume were independent predictors of lowest Sa_{O_2} during sleep (multiple R = 0·90). Figure 3 shows the relation between the lowest Sa_{O_2} during sleep and Sa_{O_2} 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 Sa_{O_2} asleep are shown in the figure. A similar relation was found between awake Sa_{O_2} measured in the clinic three weeks before the study and the lowest Sa_{O_2} during sleep (lowest Sa_{O_2} during sleep = 2·4 × awake Sa_{O_2} − 137; r^2 = 0·76).

In five patients the oxygen flow rate required to maintain Sa_{O_2} above 90% during sleep was at least 1·0 l/min more than that required to maintain Sa_{O_2} 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 maintained Sa_{O_2} 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 Sa_{O_2} measured during sleep and values obtained from a prediction equation based on Sa_{O_2} 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.[11 18 19] All but one patient in the present study, however, had REM sleep and the depth and duration of nocturnal arterial oxygen desaturation 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 associates[12] Sa_{O_2} was measured with a Hewlett Packard 47201A ear oximeter, whereas we used a Biox IIA oximeter. Recently, West and associates[20] compared the Hewlett Packard 47201A ear oximeter with the Biox III ear oximeter during rapid oscillations in Sa_{O_2} 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 Sa_{O_2} values recorded by the two oximeters was 3%. Although rapid changes in Sa_{O_2} 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 Sa_{O_2} during sleep and "awake" Sa_{O_2}[8–14] and found prediction equations similar to that of Connaughton and associates.[12] The oximeter Sa_{O_2} measured in the clinic one to three weeks before the sleep study was similar in predictive accuracy to the Sa_{O_2} measured by the oximeter with subjects sitting and awake on the night of the study (r^2 = 0·76 and 0·64 respectively). We also confirmed the relation between duration of desaturation during sleep ($TST_{<85}$) and awake Sa_{O_2},

but we found that the awake Sao_2 was a poor predictor of $TST_{<85}$ ($r^2 = 0{\cdot}53$). 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."[21] On the other hand, there is evidence that the extent of nocturnal hypoxaemia is not clinically important.[22 23] 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.[12] 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.[7] According to the prediction equation,[12] 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[12] 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.[24] 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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