Oxygen desaturation during sleep and exercise in patients with severe chronic obstructive pulmonary disease

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Patients with chronic obstructive pulmonary disease (COPD) have varying degrees of arterial oxyhaemoglobin desaturation during sleep, which have been shown to correlate with awake oxygen levels. We wished to ascertain if exercise desaturation was a better predictor of nocturnal oxygen desaturation than daytime blood gases. We studied 25 COPD patients with $PaO_2 < 10$ kPa (mean $= 8.6$ kPa), 12 of whom were normocapnic ($PaCO_2 \leq 6$ kPa, Group A), and 13 of whom were hypercapnic ($PaCO_2 > 6$ kPa, Group B), by means of overnight oximetry and maximum treadmill exercise testing. The overall group desaturated significantly more during sleep than exercise [12.9 ± 10.5 fall in nocturnal oxygen saturation ($SaO_2$) vs. 4.5 ± 3.7, $P<0.01$], Group B had a lower minimum $SaO_2$ during sleep than Group A (74.3 ± 13.4 vs. 84.6 ± 5.8, $P<0.05$), despite very similar pre-sleep $SaO_2$ (91.9 ± 3.2 vs. 92.8 ± 2.9, $P=$ n.s.). Awake $SaO_2$ correlated well with both mean values ($r=0.7$, $P<0.001$), and minimum sleep $SaO_2$ ($r=0.44$, $P<0.05$), but not with the fall in sleep $SaO_2$ ($r=0.21$, $P=$ n.s.). Minimum sleep and exercise $SaO_2$ were also significantly correlated ($r=0.44$, $P<0.05$), but the fall in $SaO_2$ during sleep and exercise was not ($P=$ n.s.). We conclude that exercise studies add no extra information to awake blood gas analysis in predicting the likelihood of nocturnal oxygen desaturation in patients with COPD.

Introduction

Oxygen desaturation is known to occur during sleep in patients with chronic obstructive pulmonary disease (COPD), particularly during rapid eye movement (REM) sleep (1–5). This desaturation may predispose to nocturnal death (6), and may also contribute to the development of pulmonary hypertension (7). Awake arterial oxygen tension ($PaO_2$) correlates with nocturnal oxygen saturation ($SaO_2$) (4,8,9,10), but recent studies have also documented significant oxygen desaturation in patients with only mild daytime hypoxaemia (5). Exercise may also lead to hypoxaemia in patients with COPD (11,12), and while a previous study has examined haemodynamic variables during sleep and exercise in COPD (13), there are no published studies examining potential relationships between oxygen desaturation during sleep and exercise in such patients.

The mechanisms leading to oxygen desaturation are likely to differ during sleep and exercise, with hypoventilation and changes in ventilation–perfusion relationships being important mechanisms during sleep (1,4,14,15,16), whereas increased airflow resistance and inadequate ventilatory response to exercise, in addition to dead space ventilation are important factors during exercise (11,17,18). However, we hypothesised that patients with severe COPD would desaturate during both exercise and sleep, and therefore, that exercise-related desaturation might provide a useful insight into the likelihood of nocturnal desaturation.

The purpose of the present study was to compare oxygen desaturation during sleep and exercise in patients with severe COPD. We sought relationships between $SaO_2$ values during sleep and exercise, in addition to awake blood gases, and pulmonary function. We wished to determine if a knowledge of the degree of exercise-related desaturation might improve the ability to predict a likelihood of nocturnal desaturation in these patients.
Materials and Methods

Thirty patients with an established diagnosis of COPD, and fulfilling the entry criteria were studied. All were hospital inpatients convalescing from a recent non-pneumonic episode of respiratory failure (\(PaO_2 < 8\) kPa). They were studied when they were in a stable condition immediately prior to hospital discharge. At the time of the study, each patient had \(PaO_2\) less than 10 kPa, forced expiratory volume in 1 s (FEV₁) less than 1.5 l and FEV₁/forced vital capacity (FVC) less than 60%. Informed consent was obtained from all patients and the study was approved by the hospital's Ethics Committee. All patients were on bronchodilator treatment, which consisted of both oral and inhaled corticosteroids, oral theophylline, and inhaled or nebulized \(\beta\)-agonist and anti-cholinergic. No patient was on oral \(\beta\)-agonist therapy and no inhaled \(\beta\)-agonist or anti-cholinergic agent was taken for at least 6 h prior to either the sleep or exercise study.

SLEEP STUDIES

\(SaO_2\) was measured continuously during sleep and exercise using a Biox 11A ear oximeter (Biox Inc., Boulder, CO), and recorded in real time on a Biox 2100 paper recorder. The accuracy of this oximeter has been well validated (19), and all patients in the present study were white. Baseline or pre-sleep \(SaO_2\) was taken as the mean \(SaO_2\) for the first 20 min after the start of monitoring, while the patients were awake and supine. Mean nocturnal \(SaO_2\) was taken as the mean \(SaO_2\) from lights-out to final morning awakening, averaged at 2 min intervals. The minimum nocturnal \(SaO_2\) that was maintained for at least 30 s was noted, and this value was subtracted from the pre-sleep \(SaO_2\) to give the maximum fall in nocturnal \(SaO_2\). The patients were observed by medical and nursing personnel to assess sleep quality, and they were well acclimatized to the hospital environment by the time of the study. Only data from nights where the sleep was judged to be good by both the patient and observer was utilized. Patients with features suggestive of sleep apnoea, such as a history of loud snoring or daytime sleepiness, or repetitive dips in their \(SaO_2\) tracing, were excluded.

EXERCISE TESTING

The exercise test was performed on the afternoon after the sleep study. Blood gases (ABGs) were drawn from the radial artery and spirometry performed immediately before the exercise test. An incremental treadmill exercise test was utilized, following the modified Naughton protocol (20) which allows for a gradual increase in exercise intensity, suitable for patients with respiratory impairment. Exercise commenced at a zero gradient and treadmill speed of 1 mile h\(^{-1}\) for 2 min. The work load was increased every 2 min with a progressive increase in speed and degree of elevation to a potential maximum of 3 mile h\(^{-1}\) at 15 degrees elevation over 20 min. The patients were encouraged to exercise to exhaustion. \(SaO_2\) and heart rate were continuously monitored during exercise. The pre-exercise \(SaO_2\) was taken as the stable \(SaO_2\) reading immediately prior to exercise. The minimum exercise \(SaO_2\) was taken as the lowest \(SaO_2\) reached, and where \(SaO_2\) rose during exercise the highest level reached was noted. The difference between the pre-exercise \(SaO_2\) and the lowest exercise \(SaO_2\) (or highest) was taken as the fall (or rise) in exercise \(SaO_2\).

STATISTICAL ANALYSIS

The relationships between continuous variables were analysed by linear regression, and the independent \(t\)-test was used to compare means where there were two independent samples of continuous data. The Chi-Squared or Fisher's Exact test were used to compare proportions of categorical data. A significance level of less than 0.05 was taken as significant, and data are presented as mean ± 1 standard deviation (SD).

Results

The data for 25 patients were included in the analysis (16 males, 9 females). Five patients were excluded from the analysis because of unsatisfactory sleep quality, or the presence of artefacts or tracings suggestive of an associated sleep apnoea (repetitive transient \(SaO_2\) dips) on their overnight \(SaO_2\) tracings. Anthropometric, spirometric and blood gas data for the 25 included patients are presented in Table 1, which also provides details of changes in \(SaO_2\) during sleep and exercise, among hypercapnic and normocapnic patients.

There was a wide variability in the maximum degree of overnight desaturation (range 3–52% fall in \(SaO_2\) from baseline). However, most of these steep falls in \(SaO_2\) were relatively brief, and the mean nocturnal \(SaO_2\) was 91% (range 78–95%). These data indicate a relatively mild degree of oxygen desaturation during sleep in this group of patients. In fact, nine patients had a mean nocturnal \(SaO_2\) the same or slightly higher than their pre-sleep \(SaO_2\).

There was, however, a substantially greater fall in \(SaO_2\) during sleep than exercise [12.9(10.5) vs. 4.5(3.7)%, \(P<0.01\)]. While the duration of exercise
was brief [mean 132(104) s], patients were encouraged to exercise to exhaustion, and all discontinued exercise because of severe dyspnoea. Two patients had a rise in SaO₂ on exercise, while it was unchanged in two others. These four patients who did not desaturate during exercise had a mean nocturnal fall in SaO₂ of 7.8% (range 4-12%) and furthermore, several patients who had minimal falls in SaO₂ during exercise had quite marked drops in nocturnal SaO₂ (e.g. 4% on exercise, 24% during sleep). The maximal heart rate on exercise was 138(15) beats min⁻¹.

Among the group of 25 patients, 12 had PaCO₂ ≤ 6 kPa (normocapnic, Group A) and 13 had PaCO₂ >6 kPa (hypercapnic, Group B). The findings during sleep and exercise among these two groups of patients are outlined in Table 1. Fortuitously, these two groups had similar daytime PaO₂, in addition to similar pre-sleep and pre-exercise SaO₂, although Group B had more severe airways obstruction. Despite similar awake PaO₂ and SaO₂ however, patients with hypercapnia desaturated significantly more than those with normal PaCO₂ during both sleep (P<0.05) and exercise (P<0.02). Seven of 12 Group A patients maintained their SaO₂ at baseline levels during sleep, while only two of Group B did so (P<0.01 by two-tailed Fisher’s Exact Test). Furthermore, 12 of 13 Group B patients had a minimum nocturnal SaO₂ of 85% or less, while only five out of 12 Group A patients did so (P=0.01 by two-tailed Fisher’s Exact Test). The duration of exercise and maximum heart rate during exercise was similar in the two groups (Table 1).

We separately examined the data for a subgroup of six patients who had more severe daytime hypoxaemia [PaO₂ <8.0 kPa, mean PaO₂ = 7.2(0.27)kPa, mean PaCO₂ =6.3(1.0)kPa]. The findings in this subgroup with respect to comparisons of sleep and exercise desaturation were similar to the overall patient group. They had a substantially lower minimum SaO₂ during sleep than exercise [76.3(6.2)% vs. 85.2(5.3)%, P<0.01].

The correlation of SaO₂ with resting, awake blood gases and pulmonary function during both sleep and exercise, is outlined in Table 2. Awake PaO₂ and SaO₂ correlated well with mean nocturnal SaO₂, similar to several previous reports (4,8-10). However, we found a lesser correlation between awake oxygen levels, and both minimum nocturnal SaO₂ and the maximum fall in SaO₂ from awake values. Daytime PaCO₂ was not correlated with any nocturnal SaO₂ variable. Resting awake PaO₂ and pre-exercise SaO₂ correlated significantly with the mean and the minimum exercise SaO₂, but not with the fall in SaO₂ on exercise. Pulmonary function correlated poorly with exercise SaO₂. Neither awake PaO₂ nor FEV₁ correlated significantly with exercise duration.
Table 2 Correlation of sleep and exercise SaO₂ with resting awake variables

<table>
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<tr>
<th></th>
<th>Age</th>
<th>Weight</th>
<th>FEV₁</th>
<th>PaO₂</th>
<th>PaCO₂</th>
<th>SaO₂†</th>
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</thead>
<tbody>
<tr>
<td><strong>Sleep</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Mean SaO₂</td>
<td>-0.37</td>
<td>-0.55**</td>
<td>0.33</td>
<td>0.54**</td>
<td>-0.36</td>
<td>0.69***</td>
</tr>
<tr>
<td>Minimum SaO₂</td>
<td>-0.29</td>
<td>-0.54**</td>
<td>0.38</td>
<td>0.35</td>
<td>-0.35</td>
<td>0.44*</td>
</tr>
<tr>
<td>Fall in SaO₂</td>
<td>0.23</td>
<td>0.48*</td>
<td>-0.40*</td>
<td>-0.23</td>
<td>0.34</td>
<td>-0.21</td>
</tr>
<tr>
<td><strong>Exercise</strong></td>
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<td></td>
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<tr>
<td>Mean SaO₂</td>
<td>0.07</td>
<td>-0.33</td>
<td>0.34</td>
<td>0.44*</td>
<td>-0.32</td>
<td>0.90***</td>
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<tr>
<td>Minimum SaO₂</td>
<td>-0.01</td>
<td>-0.30</td>
<td>0.37</td>
<td>0.45*</td>
<td>-0.51**</td>
<td>0.67***</td>
</tr>
<tr>
<td>Fall in SaO₂</td>
<td>-0.01</td>
<td>0.07</td>
<td>-0.19</td>
<td>-0.07</td>
<td>0.46*</td>
<td>-21</td>
</tr>
</tbody>
</table>

Data are correlation coefficients. SaO₂† represents resting awake SaO₂ either pre-sleep or pre-exercise as appropriate. Levels of significance: *P<0.05, **P<0.01, ***P<0.001.

Fig. 1 Comparison of the minimum SaO₂ during sleep and exercise.

Nocturnal and exercise desaturation were also compared, to see whether exercise desaturation correlated better with nocturnal SaO₂ than pulmonary function tests or daytime blood gases. The mean and minimum nocturnal and exercise SaO₂ were significantly correlated (r=0.51, P<0.05 and r=0.44, P<0.05, respectively, Fig. 1), but there was only a trend for the fall in exercise SaO₂ to correlate with the fall in nocturnal SaO₂ (r=0.37, P=n.s.).

Discussion

Previous reports have demonstrated a close association between awake PaO₂ and nocturnal oxygen desaturation, and our data broadly agree with these findings. However, the present study documents a number of novel findings with respect to sleep-related hypoxaemia in COPD, namely that (1) oxygen desaturation is greater during sleep than during maximum exercise, in patients with severe COPD, and exercise studies are no better than awake resting arterial blood gases in the prediction of nocturnal oxygen desaturation, and (2) the presence of hypercapnia increases the likelihood of nocturnal oxygen desaturation even when awake PaO₂ levels are similar among normocapnic and hypercapnic patients.

Previous authors have sought 'awake variables' that would help in the prediction of nocturnal oxygen desaturation (1,5,8–10), but there are no detailed reports which address the relationships of SaO₂ during sleep and exercise in the same group of patients with COPD, although Fletcher and co-workers make minor reference to this relationship, in a study of pulmonary haemodynamics during sleep and exercise in COPD (13). Our data indicate that exercise studies are of no greater benefit in predicting the magnitude of nocturnal oxygen desaturation than daytime blood gases.

Our data suggest that hypercapnia contributes to the development of nocturnal hypoxaemia, independent of awake PaO₂ levels (Table 1), since, fortuitously, our hypercapnic group of COPD patients had similar awake PaO₂ levels to the normocapnic group. These findings support the observations of
Bradley and co-authors (10), but, in contrast to these authors, we did not find any significant correlation between daytime PaCO\(_2\) and sleep SaO\(_2\) (Table 2). The degree of nocturnal desaturation has previously been shown to correlate with the hypercapnic ventilatory response (22), suggesting that hypercapnic patients have a greater tendency to nocturnal hypoventilation. A possible confounding factor, however, is the relatively mild degree of hypercapnia among the hypercapnic group in the present study (Table 1).

Previous reports have generally shown good correlation between daytime PaO\(_2\) or SaO\(_2\) and mean nocturnal SaO\(_2\) (4,8–10), but these variables have been found to be less accurate in predicting the minimum level of nocturnal SaO\(_2\) (5,9). Our findings agree with these previous reports, but also demonstrate that the magnitude of sleep desaturation cannot be predicted from either awake SaO\(_2\) or PaO\(_2\), and also that the magnitude of exercise desaturation does not correlate with sleep desaturation. This observation agrees with a previous study from this department among adult and adolescent patients with cystic fibrosis, performed using very similar methodology to the present study (21). This particular finding should not be surprising, however, since the baseline SaO\(_2\) must inevitably have some influence on the absolute levels of SaO\(_2\) during sleep and exercise, and thus these variables are not independent. The magnitude of desaturation from the starting awake SaO\(_2\) level is not, however, necessarily dependent on the awake level (apart from the influence of the oxyhaemoglobin-dissociation curve).

The duration of major oxygen desaturation during sleep tended to be brief. However, all except one of our patients desaturated to less than 90% for at least 5 min, and many patients had substantially greater degrees of nocturnal hypoxaemia. Fletcher and co-workers (23) have demonstrated that among COPD patients with a daytime PaO\(_2\) >60 mmHg, those who have nocturnal desaturation of less than 85% SaO\(_2\), have significantly higher pulmonary vascular resistance than those without significant nocturnal desaturation, even when the awake PaO\(_2\) levels are similar. These authors have also shown (13) that minimum sleep SaO\(_2\) was a better discriminant of increased pulmonary vascular resistance than mean sleep SaO\(_2\). Our data shows that minimum nocturnal SaO\(_2\) was significantly lower than minimum exercise SaO\(_2\) (Table 1), suggesting that among COPD patients, the greatest challenge to their cardiovascular system is at night.

Overall, the patients were unable to tolerate prolonged exercise, which may have been related to the fact that they were convalescing from an exacerbation of COPD. However, the patients were encouraged to walk for as long as possible, and all stopped the test because of severe dyspnoea or exhaustion. Furthermore, the level of exercise achieved would almost certainly be greater than that reached during normal daily activities. We recognize the possibility that patients might have responded differently due to encouragement by staff when requested to exercise to exhaustion, but feel that these differences would be similar in daily life, since one would expect that those patients who respond best to encouragement during exercise testing would also be likely to push themselves more during daily activities. It is possible that other forms of exercise testing, such as a 6 min walk might have shown different exercise tolerance.

We must recognize the possibility that the lack of formal sleep staging may have resulted in a failure to identify poor sleep quality among some of our patients. Thus we are unable to say whether all patients achieved REM sleep, which may have led us to underestimate the true degree of nocturnal desaturation among our patients. However, this should not detract from the principal findings of our study, namely that oxygen desaturation was greater during sleep than exercise, and furthermore that significant nocturnal oxygen desaturation can be found among patients with relatively normal PaO\(_2\).

We must also address the possibility that some patients with sleep apnoea syndrome were inadvertently included in the analysis, thereby exaggerating the degree of nocturnal desaturation. However, we took great care to prevent this possibility by excluding any patients with symptoms or nocturnal tracings suggestive of sleep apnoea. Patients with sleep apnoea have a typical pattern of repetitive transient dips in SaO\(_2\) during sleep, which differs markedly from the pattern of oxygen desaturation during sleep among patients with COPD (24).

We chose to examine patients who were in the convalescent phase of an exacerbation of COPD. While we recognize that such patients may not have reverted fully to their baseline functional status, this fact should not influence the comparisons made in the present study, since the comparisons between awake, sleep and exercise oxygen levels were made within a 24 h period. Furthermore, since daytime PaO\(_2\), sleep SaO\(_2\) and exercise SaO\(_2\) are all likely to be affected to a similar degree by lack of functional stability, the principal findings of the relationships between these variables are unlikely to have been affected.

We conclude from our findings that in severe COPD, sleep is associated with greater oxygen
desaturation than maximum exercise, and evaluation of exercise-induced desaturation adds little to the knowledge of resting awake Pa\textsubscript{O\textsubscript{2}} in the prediction of nocturnal desaturation.

References


