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Nocturnal Saturation Improves by Target-Flow Inspiratory Muscle Training in Patients with COPD

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Nocturnal desaturations during rapid eye movement (REM) sleep, caused by nonobstructive hypoventilation, occur frequently in patients with chronic obstructive pulmonary disease (COPD). This is partly caused by decreased activity of the intercostal and accessory muscles due to a lower motor command. The diaphragm has to compensate for the diminished activity of these muscles during REM sleep. However, in patients with COPD strength and endurance of the diaphragm may be affected by its unfavorable position on the length-tension curve because of hyperinflation. The aim of this study was to establish the causal relationship between respiratory muscle function and nocturnal saturation in patients with COPD. We hypothesized that target-flow inspiratory muscle training (TF-IMT) would improve nocturnal saturation. In 20 patients with stable COPD (FEV$_1$ 35.5 ± 14.1% of predicted) and a mean nocturnal saturation below 92% we measured maximal inspiratory pressure ($P_{\text{limax}}$), transdiaphragmatic pressure ($P_{\text{di}}$), maximal sustainable inspiratory pressure ($S_{\text{IPmax}}$), endurance time, and nocturnal saturation in Weeks 0, 4, and 10. During these 10 wk 10 patients underwent TF-IMT at 60% of $P_{\text{limax}}$ and 10 control patients received sham TF-IMT at 10% of $P_{\text{limax}}$. $P_{\text{di}}$, $S_{\text{IPmax}}$, and the endurance time as well as the nocturnal saturation improved significantly in the 60% training group (by $3.0\pm1.5$ kPa, $3.4\pm1.9$ kPa, $1.5\pm1.4$ kPa, $189\pm149$ s, and $1.9\pm2.2\%$, respectively), whereas no changes occurred in the sham training group. Also, significant correlations were observed between the changes in $P_{\text{di}}$, $S_{\text{IPmax}}$, and endurance time on the one hand and the change in nocturnal saturation on the other. We conclude that TF-IMT improves the nocturnal saturation in patients with severe COPD by increasing respiratory muscle strength and endurance. Heijdra YF, Dekhuijzen PNR, van Herwaarden CLA, Folgering HTHM. Nocturnal saturation improves by target-flow inspiratory muscle training in patients with COPD. AM J RESPIR CRIT CARE MED 1996;153:260-5.
Pulmonary medication, as shown in Table 2, was not changed during the study period. The proximal opening of the esophageal lumen 38 cm from the nares. The catheter was perfused with water at a constant flow rate of 99 ml/h. The pressure generated by the water flow was 1.2 kPa. The proximal ends of the double-lumen catheter were connected to two pressure transducers. The zero reference point was arbitrarily set as the pressure measured at functional residual capacity (FRC). Pdi was calculated by subtracting esophageal pressure (Pes) from gastric pressure (Pga). Pimax, PEmax, Pes, and Pga were displayed on a chart recorder (BD101; Kipp & Zonen, Delft, the Netherlands). Pdi was measured with visual feedback on the chart recorder and the patients were encouraged to generate the highest deflections. LaPorta and Grassino (17) showed that in this way the highest Pdi values were obtained in patients with COPD. Pressure measurements were performed in sitting position, with the subjects wearing a noseclip.

Pmax (from residual volume, RV) and PEmax (from TLC) were repeated until three reproducible measurements had been performed with a maximal variability of 10% (17). The highest values were used for analysis. For the sake of convenience, Pmax was expressed as an absolute value. Predicted values for Pmax and PEmax were calculated according to Wilson and colleagues (15).

Respiratory muscle endurance was measured using a device similar to that described by Nickerson and colleagues (18). Patients inspired against a fixed inspiratory resistance. They had to generate a certain threshold pressure (Pth) to lift the plunger and allow air to flow. Pth could be varied by adding weight to the plunger. Pth was measured inside the mouthpiece with a pressure transducer. There was a linear relationship between Pth and the weight on the plunger. The patients started with a load of about 10% of their Pmax and 25- or 50-g weights were added at 1.5-min intervals (19). They continued to breathe until they could no longer inspire. The total time they were able to breathe through the incremental threshold device was defined as the endurance time. The pressure achieved during the heaviest load tolerated for at least 45 s was defined as the maximal sustainable inspiratory pressure (SIPmax) (19).

Nocturnal recordings. During the night oxygen saturation and heart rate were measured in a real-time format by a pulse oximeter (Oxyhuttle; Sensor Medics, Anaheim, CA). The data were stored and digitized. CO2 measurements were obtained during both mouth and nasal breathing. Because carbon dioxide analysis was performed with a closed-circuit helium-dilution method, the data were not adjusted for barometric pressure changes. The baseline Sao2 awake was defined as the mean saturation during the first 15 min of the record, when the patient was awake and lying flat (20). Desaturation was defined as a decrease by more than 4% in oxygenation from the baseline saturation awake, for a period of 5 min or more. This definition was derived from the study of Block and colleagues (21) who described that a desaturation was clinically noteworthy when it fell from 90 to 86% in more than 10 s or from a fall of 4% or more occurred and from the study of Fletcher and colleagues (22) who defined a nocturnal desaturation as a fall below 90% lasting at least 5 min.

End-tidal Pco2 (PetCO2) was measured with a sampling cannula (Mijnhierh Capnolyser, Bilthoven, the Netherlands) by introducing a catheter into the nasopharyngeal cavity through a nostril. In this way PetCO2 was monitored during both mouth and nasal breathing. Because PetCO2 is not representative of arterial PCO2 increases in PetCO2, it was only used qualitatively as indicators of hyperventilation in combination with the saturation and thoracic movement signals (22).

Thoracic movements were measured by means of respiratory inductive plethysmography (Vitalog, Bear Island, CA), which was used to indicate if there was respiratory activity at all (23).

An electro-oculogram (EOG) was performed with surface electrodes. The EOG signal was used for visual scoring of wakefulness, non-REM and REM sleep (23). When rapid eye movements were present in combination with desaturations, it was even more likely that REM sleep was present (24). Oxygen saturation, heart rate, thoracic movement, electro-oculogram and PetCO2 signals during the night were displayed on a six-channel chart recorder (BD101; Kipp & Zonen, Delft, the Netherlands). The next morning the nocturnal recordings were analyzed by a technician of the lung function laboratory who was unaware of the treatment modality. At least one episode of REM sleep should be present before accepting the nocturnal registration as representative. The St. Mary's Hospital sleep questionnaire was used for assessing the quality of sleep during the preceding night (25).

Lung function and blood gas analysis. Lung function tests were performed with a wet spirometer and by a closed-circuit helium-diffusion

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**Table 2: Pulmonary Medication**

<table>
<thead>
<tr>
<th>Medication</th>
<th>TF-IMT 60% Pmax (no. patients)</th>
<th>TF-IMT 100% Pmax (no. patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled beta agonists</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Inhaled anticholinergics</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Oral corticosteroids, 5–10 mg</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>Oral theophyllines</td>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>
method (Pulmonet III; Sensormedics, Bihoven, the Netherlands). Diffusion capacity (Kco) was measured by the single breath-holding carbon monoxide method (Sensormedics 2450). Predicted spirometric values were taken from European Respiratory Society standards (26).

Arterial blood gas samples were taken in semirecumbent position at 9:00 A.M., after the patients had been lying down for at least 15 min (Corning Ph 127).

Statistical Analysis

Data are expressed as mean ± standard deviation (SD). The Wilcoxon signed rank test was performed to test differences within the groups after 10 wk of TF-IMT at 60% or 10% of Pimax. The Mann-Whitney U test was used to test the difference between the two groups after training. The Spearman correlation test was used to analyze correlations between changes in respiratory muscle performance and changes in nocturnal saturation. A p value < 0.05 was considered significant. For all analyses the SAS package (SAS Institute Inc., Cary, NC) was used.

RESULTS

Patients

Ten patients (3 female) underwent TF-IMT at 60% and 10 patients (2 female) received sham TF-IMT at 10% of their Pimax. There were no significant differences in age, body mass index, lung function, and daytime arterial blood gases between the groups (Table 1). During the training period, daytime blood gases did not change in the 60% Pimax group, whereas PaO₂ decreased by 0.7 kPa in the 10% Pimax group. PaCO₂, FEV₁, and FRC did not change in either group. All patients finished the complete study period.

Effects of IMT on Maximal Respiratory Pressures and Endurance

Table 3 shows the effects of 10 wk TF-IMT on respiratory muscle performance. In both groups Pdi could not be measured in three patients because they were not able to swallow the double-lumen catheter. Pimax, Pdi (Figure 1), SIPmax, and the endurance time increased significantly in the 60% training group, while no change was seen in the 10% sham training group. For all parameters there was a significant difference between the training group and the control group. Pimax improved significantly in the 60% Pimax group (1.3 ± 2.3 kPa). There was also a significant difference in Pmax between the two groups.

Effects of Increased Respiratory Muscle Strength and Endurance on Nocturnal Saturation

In the 60% Pimax group the mean subjective sleep time, assessed by the St. Mary's hospital sleep questionnaire, was 4.7 ± 1.3 h and 5.3 ± 1.5 h in Week 0 and 10, respectively. In the 10% Pimax group, the patients slept 4.8 ± 1.2 and 4.7 ± 1.6 h, respectively.

The effects of TF-IMT on nocturnal parameters are shown in Table 4. All desaturations were of the nonobstructive type and were caused by hypventilation. After 10 wk of TF-IMT, NSao₂ increased significantly by 1.9 ± 2.2% in the 60% Pimax group, while it decreased by 0.9 ± 1.5% in the control group (p = 0.16). A significant difference of 2.8% developed between the two groups (Figure 2). A significant increase of 3.3 ± 4.8% in the lowest saturation was observed in the 60% Pimax group. In the control group no significant difference developed (p = 0.19). The difference in the lowest NSao₂ between the two groups was significant (Figure 3). The percentage of recording time during which patients were desaturated decreased by 13.2 ± 13.5% in the 60% Pimax group (p < 0.05). In the 10% Pimax group no change occurred (p = 0.68). The difference between the groups was significant (Figure 4). Also the percentages of recording time during which patients were hypoxemic (SaO₂ < 90%) (14) before and after TF-IMT were compared. A large improvement was observed: in the 60% Pimax training group the percentage of recording time spent at a saturation below 90% decreased from 55.5 ± 42.3% to 28.4 ± 35.0%, while in the sham training group the saturation remained below 90% during a large part of the night (59.1 ± 40.3% and 62.5 ± 37.6%, respectively) (Figure 5). In addition, at the start of the study seven of the 10 patients in the 60% Pimax training group experienced periods with a saturation below 85% at the start of the study seven of the 10 patients in the 60% Pimax training group experienced periods with a saturation below 90% (range 0.4 to 90% recording time, mean 18.7 ± 33.2%). The time spent below 85% SaO₂ decreased in all these patients after TF-IMT, but the largest improvement was observed in the two patients with the most severe desaturations. In these patients the recording time spent below 85% SaO₂ decreased from 20.8% and from 71.2 to 3.0%, respectively.

Correlations between Respiratory Muscle Function and Nocturnal Saturation

Significant correlations were found between the change in mean nocturnal SaO₂ and the change in Pdi (r = 0.67, p < 0.01), SIPmax (r = 0.54, p < 0.05), and the endurance time (0.53, p < 0.05). The correlation coefficient between the change in mean NSao₂ and the change in Pimax was 0.43 (p = 0.06).

DISCUSSION

The present study shows that TF-IMT at 60% of Pimax improves static maximal inspiratory mouth pressure, static maximal inspiratory transdiaphragmatic pressure, and respiratory muscle performance.*
endurance in patients with severe COPD. This improvement in respiratory muscle function appears to result in an increase of the mean and lowest nocturnal saturation, a decrease of the percentage of time desaturations occurred, and a reduction of time spent below a SaO₂ of 90%, compared with the control group which received sham training at 10% Pimax. These changes suggest that respiratory muscle function plays a role in nocturnal saturation in patients with COPD.

The results of inspiratory muscle training in patients with COPD are conflicting. Some studies showed an increase in Pimax and endurance (11–13), but this was not confirmed by other investigators (27–29). In these latter studies inspiratory flow, breathing pattern, and inspiratory pressure were not defined, probably resulting in an inadequate training stimulus (27–29). Therefore, in the present study the breathing pattern (inspiration time 3 s, expiration time 4 s) as well as the target flow at a fixed inspiratory resistance, resulting in a fixed inspiratory pressure (60% or 10% Pimax), were explicitly defined. As far as we know, the improvement of Pdi by inspiratory muscle training (Figure 1) has not been described before.

Pmax increased significantly by 1.3 kPa in the 60% training group and a significant difference was noticed between the two groups. This might be explained by the fact that, before performing an inspiratory maneuver during TF-IMT, patients were encouraged to expire as far as possible to make it easier to generate the required pressure. This was done because the highest inspiratory pressures can be generated at RV with a gradual decrease at increasing lung volumes (30). It may therefore be speculated that expiratory muscles were also trained to some extent during TF-IMT. In the present study, Pmax and Pdi were measured from RV instead of FRC, because the predicted values for Pmax according to Wilson and colleagues (15) were also measured at RV. This overestimates Pmax because of the elastic recoil pressure of the lung and chest wall.

The increase in mean nocturnal SaO₂ (Figure 2) could not be explained by an increase in daytime Pao₂ or FEV₁, because these parameters remained unchanged in the 60% training group. Therefore, the improved nocturnal saturation may be a direct consequence of the improved respiratory muscle performance. This is supported by the significant correlation coefficients found between the change in respiratory muscle function and the change in mean nocturnal SaO₂. The improvement of Pdi is then likely to cause a decrease in desaturation time (Figure 3) and an increase in the lowest nocturnal SaO₂ (Figure 4) resulting in an increase of the mean nocturnal saturation (Figure 2).

Electroencephalography was not performed in this study, so it was not possible to obtain classical sleep staging. However, eye movements taken from EOG are sufficiently characteristic to allow visual scoring of wakefulness, non-REM and REM sleep (23). During the study, the time spent in non-REM and REM sleep stages by the patients did not change.

An acclimatization night was not used because most patients

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**TABLE 4**

**NOCTURNAL RECORDING DATA**

<table>
<thead>
<tr>
<th>TF-IMT</th>
<th>60% Pmax</th>
<th>TF-IMT</th>
<th>10% Pmax</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Week 0</td>
<td>Week 10</td>
<td>Week 0</td>
</tr>
<tr>
<td>Time in bed, min</td>
<td>474 ± 29</td>
<td>466 ± 38</td>
<td>466 ± 33</td>
</tr>
<tr>
<td>REM sleep, min</td>
<td>47 ± 19</td>
<td>46 ± 20</td>
<td>48 ± 19</td>
</tr>
<tr>
<td>Non-REM sleep, min</td>
<td>255 ± 42</td>
<td>263 ± 50</td>
<td>242 ± 40</td>
</tr>
<tr>
<td>NSaO₂, %</td>
<td>88.8 ± 3.0</td>
<td>90.7 ± 1.7</td>
<td>* p &lt; 0.05</td>
</tr>
<tr>
<td>Lowest NSaO₂, %</td>
<td>80.3 ± 9.6</td>
<td>83.6 ± 7.8</td>
<td>* p &lt; 0.01</td>
</tr>
<tr>
<td>% Time des, %</td>
<td>18.6 ± 18.0</td>
<td>5.4 ± 18.0</td>
<td>17.4 ± 27.8</td>
</tr>
<tr>
<td>SaO₂ &lt; 90%, % time</td>
<td>55.5 ± 42.3</td>
<td>28.4 ± 35.0</td>
<td>59.1 ± 40.3</td>
</tr>
</tbody>
</table>

Definition of abbreviations: TF-IMT = target-flow inspiratory muscle training; Pmax = maximal inspiratory mouth pressure; REM = rapid eye movement; NSaO₂ = mean nocturnal arterial oxygen saturation; % time des = percentage of recording time patients were desaturated; lowest NSaO₂ = lowest nocturnal arterial oxygen saturation; SaO₂ < 90%, % time = percentage of recording time patients had a saturation below 90%.

* Data are expressed as means ± SD.
† p < 0.05 within the group.
‡ p < 0.01.
§ p < 0.01.

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**Figure 2.** Effects of TF-IMT on mean nocturnal saturation (NSaO₂). Closed squares represent 60% Pmax group; open circles represent 10% Pmax group. *p < 0.05 within 60% Pmax group; **p < 0.01 between the two groups.

**Figure 3.** Effects of TF-IMT on the lowest nocturnal saturation. Closed squares represent 60% Pmax group; open circles represent 10% Pmax group. *p < 0.05 within 60% Pmax group; #p < 0.05 between the two groups.
Figure 4. Effects of TF-IMT on the percentage of recording time patients were desaturated. Closed squares represent 60% Pimax group; open circles represent 10% Pimax group. *p < 0.05 within 60% Pimax group; \#p < 0.05 between the two groups.

Figure 5. Effects of TF-IMT on the percentage of recording time the patient's Sao2 was lower than 90%. Each set of dots, connected by a line, represents one patient. *p < 0.05 within 60% Pimax group; \#p < 0.05 between the two groups.

had undergone a nocturnal registration before and were accustomed to the procedure. Stradling and colleagues (2) showed that the mean and lowest nocturnal saturation during consecutive nights were very similar in patients with COPD. Similar findings were observed by Gothe and colleagues (31), who studied the oxygen saturation and breathing pattern during two nonconsecutive nights in patients with COPD. In our control group the mean and lowest nocturnal Sao2 as well as the percentage of time patients were desaturated did not change either during the study. In addition, the amount of REM sleep remained constant.

The present study was performed in a single-blind fashion, but the nocturnal recordings were analyzed by a technician of the lung function laboratory who was unaware of the treatment modality. In addition, the respiratory muscle measurements were performed without knowledge about the nocturnal saturation data.

The course of the present study was too short and it was not designed to evaluate the influence of increased NSAo2 or decreased desaturation time on polycythemia, cor pulmonale, cardiac arrhythmias, and survival. However, in studies with a comparable percentage of desaturation time, adverse clinical effects were found. In the study of Levi-Valensi and colleagues (32), a correlation (r = 0.33) between the total duration of saturation dips and pulmonary hypertension in 40 patients with COPD (daytime Pao2 8.0 to 9.3 kPa) was found. A desaturation was defined as a fall of > 4% from the baseline awake value. The mean nocturnal desaturation time was 56 min. These investigators also showed that pulmonary hypertension was only present in 6 of 18 patients in the desaturation group. In these 18 patients the desaturation time was 105 min. In the 22 nondesaturation patients no pulmonary hypertension was present. These findings correspond with the data published by Fletcher and colleagues (33). These researchers found that the pulmonary arterial pressure was significantly higher in desaturating (n = 36) than in non-desaturating (n = 13) patients with COPD and a daytime Pao2 > 60 mm Hg. The mean nocturnal desaturation time in the desaturating patients was 56 min. So, although we did not measure pulmonary arterial pressure in our patients, pulmonary hypertension was likely to be present in at least some of our patients, because the desaturation time in our study (88 min) is comparable to the desaturation time in the aforementioned studies in which pulmonary hypertension was found. To our knowledge, no placebo-controlled studies have been published on the effects of a decrease in desaturation time, induced by oxygen, respiration stimulating medication or training, on the pulmonary artery pressure. As a consequence, the question of whether a decrease in desaturation time as found in the present study to some extent reverses its clinical sequelae cannot be answered directly.

The data on effects of nocturnal hypoxemia on survival are conflicting and difficult to compare. Connaughton and colleagues (20) found in 97 patients with COPD (FEV1 24.9 ± 9.0% of predicted, Pao2 55 ± 10 mm Hg) that patients who were more hypoxemic at night than predicted from the regression relationship during the day, had a survival similar to that of the patients who were less hypoxemic than predicted. In the regression relationship, daytime Sao2 was the only predictive variable. The authors concluded that the severity of nocturnal hypoxemia did not influence the prognosis. However, in their study many patients were already hypoxic during the day, so that effects of nocturnal hypoxemia alone on survival could not be estimated. In contrast, Fletcher and coworkers (34) showed in 169 patients with COPD (FEV1 35% of predicted, who were all normoxemic [daytime Pao2 > 60 mm Hg]) that desaturating patients (mean desaturation time [below 90% Sao2] 134 min) had a worse survival than non-desaturating patients (mean survival 2.9 ± 1.7 and 3.7 ± 1.7 yr, respectively). Furthermore, 5-yr survival was also significantly greater in the non-desaturating group. The effects of oxygen on survival in the desaturating group showed a trend toward shorter survival in the non-oxygen-treated group. However, these investigators did not describe the amount of oxygen administered nor the effects of oxygen on nocturnal saturation.

The increase of 1.9 ± 2.2% in the mean nocturnal saturation and the substantial decrease in desaturation time (13.2 ± 13.5%) in the 60% Pimax training group in our study might be of clinical importance, since the complications of nocturnal hypoxemia as mentioned earlier were described especially in desaturating patients. In addition, the time spent below 90% Sao2 during the night was significantly reduced (Figure 5). This reduction might possibly reduce the risk of developing pulmonary hypertension during the night.

In conclusion, this study shows that TF-IMT at 60% of Pimax improves the nocturnal saturation in patients with COPD. This improvement is caused by an increased Pimax and Pdi in particular as well as an increased respiratory muscle endurance.

Acknowledgment: The writers thank Th. M. de Boo and W. A. J. G. Lemmens of the Medical Statistical Department for their statistical advice and the technicians of the lung function department, Medical Centre Dekkerswald, for their measurements.

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Heijdra, Dekhuijzen, van Herwaarden, et al. TF-IMT Improves Nocturnal Saturation


