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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 (FEV₁ 35.5 ± 14.1% of predicted) and a mean nocturnal saturation below 92% we measured maximal inspiratory pressure (Pimax), transdiaphragmatic pressure (Pdi), maximal sustainable inspiratory pressure (SIPmax), endurance time, and nocturnal saturation in Weeks 0, 4, and 10. During these 10 wk 10 patients underwent TF-IMT at 60% of Pimax and 10 control patients received sham TF-IMT at 10% of Pimax. Pdi, SIPmax, and the endurance time as well as the nocturnal saturation improved significantly in the 60% training group (by 3.0 ± 1.5 kPa, 3.4 ± 1.9 kPa, 1.5 ± 1.4 kPa, 189 ± 149 s, and 1.9 ± 2.2%, respectively), whereas no changes occurred in the sham training group. Also, significant correlations were observed between the changes in Pdi, SIPmax, 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.

Many patients with severe chronic obstructive pulmonary disease (COPD) have low arterial oxygen saturation during the night (1, 2). The most important reason for nocturnal desaturations in these patients is hypoventilation (3). The most pronounced falls in saturation occur during REM sleep (2), because in this sleep stage skeletal postural muscle tone and the activity of intercostal and accessory respiratory muscles are decreased (4, 5). This is caused by supraspinal inhibition of gamma motorneurons, and presynaptic inhibition ofafferent terminals of muscle spindles. The diaphragm escapes from reduction of activation during REM sleep, because it is almost exclusively driven by alpha motorneurons. It has considerably fewer muscle spindles than intercostal muscles and has little postural activity (6).

In patients with COPD, however, strength and endurance of the diaphragm may be affected by its unfavorable position on the length-tension curve because of hyperinflation and other factors such as hypoxemia, hypercapnia, and the use of corticosteroids (7–9). In a former study, we found a significant correlation between respiratory muscle strength (maximal inspiratory mouth and transdiaphragmatic pressures) and nocturnal saturation (10). However, it is not known if this is a causal relationship. Because inspiratory muscle training can improve respiratory muscle strength (11–13), this may possibly lead to higher nocturnal saturations.

Therefore, the aim of this study was to answer the physiologic question of whether there is a causal relationship between respiratory muscle dysfunction and nocturnal saturation. It was hypothesized that target-flow inspiratory muscle training (TF-IMT) should result in improved nocturnal saturation by increased respiratory muscle strength and in particular diaphragm strength, in patients with severe COPD.

METHODS

Study Design and Training

In a single-blind intervention study the effects of TF-IMT on respiratory muscle performance and nocturnal saturation data were compared with sham TF-IMT in 20 patients with COPD. Informed consent was obtained from all patients. The study was approved by the Hospital Medical Ethics Committee.

Inspiratory muscle training was performed at home, daily during two periods of 15 min using an incentive flow meter (Inspirx; Respincare Medical Inc., the Hague, the Netherlands) with an added resistance in the mouthpiece (12). Instruction on how to use the training device was...
given by one of the investigators. The patients had to generate an inspiratory flow rate at which the ball in the flow meter reached the top of the device (target flow). The expiration was unloaded. The adjustable leak in the flow meter was set so that the patients had to generate either 60% or 10% of their maximal inspiratory mouth pressure to attain the target flow. Every week, a physiotherapist of our institute checked if the maneuvers were performed correctly. Maximal inspiratory pressure (P|max) was measured every week. If it was changed, the leak was adjusted according to the new P|max. The inspiratory and expiratory times were set at 3 s and 4 s, respectively.

Patients

Twenty patients with COPD (five female), according to the standards of the American Thoracic Society (14), were selected if their mean nocturnal arterial oxygen saturation was lower than 92%. All patients were in a stable condition at the time of study as defined by a fluctuation in FEV1 of less than 10% in the preceding 6 mo. Patients with other pulmonary diseases, chest wall deformations, a previous thoracotomy, diabetes mellitus, neuromuscular diseases, obstructive sleep apnea syndrome, or an overlap syndrome were excluded. None used medication that stimulated or depressed respiration. The patients were randomized to receive either TF-IMT at 60%, or sham training at 10% of their Pimax during 10 wk. Evaluation was performed in Weeks 0, 4, and 10. Patient characteristics and lung function data are summarized in Table 1. Pulmonary medication, as shown in Table 2, was not changed during the study period.

Measurements

Pressure measurements (force and endurance). Maximal inspiratory and expiratory mouth pressures (Pmax) were measured with a device based on that used by Wilson and colleagues (15). A small leak (internal diameter 1.1 mm, length 40 mm) in the mouthpiece prevented the buccal muscles from producing significant pressures and from closing the glottis. The pressure inside the mouthpiece was measured with a pressure transducer (model DP103-32; Validyne, Northridge, CA; range ± 50 kPa). Transdiaphragmatic pressure (Pdi) was measured with a flexible double-lumen catheter (internal diameter of each lumen 1.1 mm) introduced through the nose (16). The catheter was positioned with the distal opening of the gastric lumen 58 cm from the nares and 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). Pmax, Pmax, 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 Pes 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 Pmax 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 weighted plunger. They had to lift 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 (Oxyshunt; Sensor Medics, Anaheim, CA). The data were stored and digitized. Computerized analysis provided mean nocturnal saturation (NSao2), standard deviation, and a histogram of the distribution of % SaO2 values. 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 a fall of 4% or more occurred and from the study of Fletcher and colleagues (1) who defined a nocturnal desaturation as a fall below 90% lasting at least 5 min.

End-tidal Pco2 (PetCO2) was measured with a sampling cannograph (Mijnharts Carpynol, 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 were only used qualitatively as indicators of hypventilation 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-dilution

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**TABLE 1**

<table>
<thead>
<tr>
<th>Variables</th>
<th>TF-IMT 60% Pmax</th>
<th>TF-IMT 100% Pmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>62.4 ± 8.8</td>
<td>61.8 ± 7.3</td>
</tr>
<tr>
<td>Pack-years</td>
<td>19.1 ± 7.8</td>
<td>27.1 ± 19.3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.7 ± 3.3</td>
<td>23.0 ± 3.2</td>
</tr>
<tr>
<td>TLC, % pred</td>
<td>105.0 ± 18.5</td>
<td>103.6 ± 21.7</td>
</tr>
<tr>
<td>FRC, % pred</td>
<td>130.0 ± 22.3</td>
<td>137.7 ± 40.0</td>
</tr>
<tr>
<td>FEV1, % pred</td>
<td>38.2 ± 15.1</td>
<td>32.8 ± 13.0</td>
</tr>
<tr>
<td>FEV1/FVC, % pred</td>
<td>35.6 ± 12.5</td>
<td>32.7 ± 13.0</td>
</tr>
<tr>
<td>Kco, % pred</td>
<td>47.6 ± 19.3</td>
<td>54.5 ± 22.1</td>
</tr>
<tr>
<td>PaCO2, kPa</td>
<td>8.6 ± 1.1</td>
<td>8.7 ± 1.0</td>
</tr>
<tr>
<td>PaCO2, kPa</td>
<td>6.1 ± 1.0</td>
<td>5.8 ± 0.9</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: TF-IMT = target-flow inspiratory muscle training; Pmax = maximal inspiratory mouth pressure; BMI = body mass index; TLC = total lung capacity; FRC = functional residual capacity; FEV1 = forced expiratory volume in one second; FVC = inspiratory vital capacity; Kco = diffusion capacity. Data are expressed as means ± SD.

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**TABLE 2**

<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>2</td>
</tr>
<tr>
<td>Oral corticosteroids, 5–10 mg</td>
<td>10</td>
<td>10</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 af­
fter 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 train­
ing. The Spearman correlation test was used to analyze correlations be­
tween changes in respiratory muscle performance and changes in noc­
turnal 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 pa­
tients (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 dou­
ble-lumen catheter. Pmax, 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 para­
meters there was a significant difference between the training


group and the control group. Pmax 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 hypoventilation. After 10 wk of TF-IMT, NSA02
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 NSA02 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% Pmax group no change occurred
(p = 0.68). The difference between the groups was sig­
nificant (Figure 4). Also the percentages of recording time dur­
ing which patients were hypoxicemic (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%
(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 pa­
tients with the most severe desaturations. In these patients the
recording time spent below 85% Sao2 decreased from 90.0 to
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 Pmax was 0.43 (p = 0.06).

DISCUSSION

The present study shows that TF-IMT at 60% of Pmax improves
static maximal inspiratory mouth pressure, static maximal in­
spiratory transdiaphragmatic pressure, and respiratory muscle

| TABLE 3
| RESPIRATORY MUSCLE PERFORMANCE* |
|-----------------|-----------------|
| TF-IMT | 60% Pimax | TF-IMT | 10% Pimax |
| Week 0 | Week 10 | Week 0 | Week 10 |
| Pmax, kPa | 6.2 ± 1.2 | 9.2 ± 2.0 | § | 5.6 ± 1.5 | 5.8 ± 1.4 |
| % pred | 81.7 ± 15.7 | 120.4 ± 26.8 | 73.0 ± 19.0 | 76.3 ± 18.6 |
| Pdi, kPa | 6.6 ± 1.8 | 10.0 ± 3.4 | § | 5.8 ± 1.3 | 6.0 ± 1.6 |
| Pmax, kPa | 10.4 ± 2.8 | 11.7 ± 4.0 | § | 8.5 ± 2.7 | 7.6 ± 2.8 |
| % pred | 90.3 ± 22.0 | 101.5 ± 28.3 | 73.3 ± 22.0 | 64.3 ± 21.2 |
| SIPmax, kPa | 2.9 ± 1.7 | 4.4 ± 2.3 | § | 2.3 ± 0.9 | 2.0 ± 0.8 |
| Time, s | 437 ± 209 | 626 ± 245 | § | 469 ± 223 | 419 ± 181 |

Definition of abbreviations: TF-IMT = target-flow inspiratory muscle training; Pmax = maximal inspiratory mouth pressure; Pdi = maximal inspiratory transdiaphragmatic pressure; SIPmax = maximal expiratory mouth pressure; time = endurance time.

* Data are expressed as means ± SD.
† p < 0.05.
‡ p < 0.01.
§ p < 0.001 between the two groups.

Figure 1. Effects of TF-IMT on maximal inspiratory transdiaphragmatic pressure. Closed squares represent 60% Pimax group; open circles represent 10% Pimax group. *p < 0.05 within 60% Pimax group; ##p < 0.01 between the two groups.
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 Pimax 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 60% Pimax</th>
<th>TF-IMT 10% Pimax</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time in bed, min</strong></td>
<td><strong>Time in bed, min</strong></td>
</tr>
<tr>
<td><strong>REM sleep, min</strong></td>
<td><strong>REM sleep, min</strong></td>
</tr>
<tr>
<td><strong>Non-REM sleep, min</strong></td>
<td><strong>Non-REM sleep, min</strong></td>
</tr>
<tr>
<td><strong>NSaO2, %</strong></td>
<td><strong>NSaO2, %</strong></td>
</tr>
<tr>
<td><strong>% Time des, %</strong></td>
<td><strong>% Time des, %</strong></td>
</tr>
<tr>
<td><strong>SaO2 &lt; 90%, % time</strong></td>
<td><strong>SaO2 &lt; 90%, % time</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Week 0</strong></th>
<th><strong>Week 10</strong></th>
<th><strong>Week 0</strong></th>
<th><strong>Week 10</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>474 ± 29</td>
<td>466 ± 38</td>
<td>466 ± 33</td>
<td>478 ± 23</td>
</tr>
<tr>
<td>47 ± 19</td>
<td>466 ± 20</td>
<td>48 ± 19</td>
<td>47 ± 19</td>
</tr>
<tr>
<td>255 ± 42</td>
<td>263 ± 50</td>
<td>242 ± 40</td>
<td>248 ± 47</td>
</tr>
<tr>
<td>88.8 ± 3.0</td>
<td>90.7 ± 1.7</td>
<td>88.3 ± 1.9</td>
<td>88.4 ± 2.7</td>
</tr>
<tr>
<td>80.3 ± 9.6</td>
<td>83.6 ± 7.8</td>
<td>81.7 ± 4.2</td>
<td>89.7 ± 3.0</td>
</tr>
<tr>
<td>18.6 ± 18.0</td>
<td>5.4 ± 5.4</td>
<td>17.4 ± 27.8</td>
<td>16.2 ± 23.3</td>
</tr>
<tr>
<td>55.5 ± 42.3</td>
<td>28.4 ± 35.0</td>
<td>59.1 ± 40.3</td>
<td>62.5 ± 37.6</td>
</tr>
</tbody>
</table>

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*Data are expressed as means ± SD. $^*$ **p < 0.05 within the group. $^1$ **p < 0.01. $^2$ Data are expressed as means ± SD.

---

**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.
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 desaturating group. In these 18 patients the desaturation time was 105 min. In the 22 non-desaturating 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 hypoxic at night than predicted from the regression relationship during the day, had a survival similar to that of the patients who were less hypoxic 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 normoxic [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.

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